JBUON 2020; 25(2): 1122-1129
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Can cut-off points of 10 and 15 mm of thyroid nodule predict malignancy on the basis of three diagnostic tools: i) strain elastography, ii) the Bethesda System for Reporting Thyroid Cytopathology with 27-gauge fine-needle, and iii) histopathology?

Demet Sengul[1], Ilker Sengul[2,3], Erol Egrioglu[4,5], Tuncer Ozturk[3], Ismail Aydin[3], Tugrul Kesicioglu[3], Selahattin Vural[3], Alptekin Tosun[6], Tumay Bekci[6]

[1]Department of Pathology, Giresun University Faculty of Medicine, TR28100 Giresun, Turkey; [2]Division of Endocrine Surgery, Giresun University Faculty of Medicine, TR28100 Giresun, Turkey; [3]Department of General Surgery, Giresun University Faculty of Medicine, TR28100 Giresun, Turkey; [4]Department of Management Science, Marketing and Forecasting Research Center, Lancaster University Management Science School, Bailrigg, Lancaster, LA1 4YK, United Kingdom; [5]Department of Statistics, Forecast Research Laboratory, Giresun University Faculty of Art and Science, TR28100, Giresun, Turkey; [6]Department of Radiology, Giresun University Faculty of Medicine, TR28100 Giresun, Turkey.

Summary

Purpose: *This study evaluated whether the cut-offs 10 and 15 mm can help distinguish malignant from benign nodules regarding three diagnostic tools: i) strain elastography (SE), ii) the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), iii) histopathology.*

Methods: *From 2012 to April 2015, a retrospective analysis was conducted by enrolling the data of 425 consecutive eligible patients with 500 thyroid nodules. The efficacy of the nodule size, as of the cut-offs, on the estimation for malignancy had been analysed on the basis of the three diagnostic tools.*

Results: *Of the 500 thyroid nodules examined, 80 (16.0%) were under 10 mm and 420 (84.0%) were over 10 mm in diameter. No significant difference was found between over 10 mm with i) TES (Tsukuba Elasticity Score) 4 and 5, area under the curve (AUC) 0.531, ii) TBSRTC (The Bethesda System for Reporting Thyroid Cytopathology) III, IV, V, VI, undetermined and malignant cytology, AUC 0.517, iii) malignant histopathology, AUC 0.509. Similarly, no significance difference was recognized between over 15 mm with i) TES 4 and 5, AUC 0.623, ii) undetermined and malignant cytology, AUC 0.455, iii) malignant histopathology, AUC 0.515 by McNemar test. However, size over 15 mm may strengthen the prediction among TES 4 and 5 and malignant histopathology, as weakens in undetermined and malignant cytology.*

Conclusions: *These preliminary data of 3-year single-center study suggest that assignment of 10 and 15 mm as the cut-off points of the thyroid nodules may not be predictive of malignancy on the basis of three diagnostic tools. Nevertheless, higher cut-off may corrobarate the correlation with TES 4 and 5 and malignant histopathology while attenuation with TBSRTC III, IV, V, and VI, confront with the lower one, 10 mm.*

Key words: *fine-needle aspiration, Bethesda, undetermined cytology, thyroidectomy, thyroidology, ultrasonography, elastography*

Introduction

The clinical management of thyroid nodules, particularly with undetermined cytology remains a major challenge for thyroidology. The role of ultrasound (US) elastography in this setting is still controversial [1]. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), is already the

Corresponding author: Ilker Sengul, MD. Division of Endocrine Surgery, Department of General Surgery, Giresun University Faculty of Medicine, Gazipasa Compund, Gazi Ave, TR28100 Giresun, Turkey.
Tel (Hospital): +90 454 310 20 00, Fax: +90 454 310 16 99, Email: ilker.sengul.52@gmail.com
Received: 27/08/2019; Accepted: 04/10/2019

major, primary, and principal system for reporting the thyroid fine-needle aspiration (FNA) cytology (FNAC) worldwide, which was firstly declared in 2007 at the National Cancer Institute (NCI) Thyroid Fine Needle Aspiration State of the Art and science Conference, Bethesda, Maryland, US. It is a six-tiered diagnostic system: [1] non-diagnostic, TBSRTC I; [2] benign, TBSRTC II; [3] Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) TBSRTC III; [4] Follicular neoplasm/suspicious for follicular neoplasm, TBSRTC IV; [5] suspicious for malignancy (SM), TBSRTC V; [6] malignant, TBSRTC VI. The widely used thyroid guidelines, American Thyroid Association (ATA) management guidelines 2009 [3] and also 2015 [4], have endorsed the utilization of TBSRTC for the assessment and interpretation of the thyroid cytopathology. Sonoelastography as firstly designed by Ophir et al [5], School of Medicine, University of Texas, Houston, US, 1991, was utilized to advance the aptitude of diagnostic accuracy for the thyroid nodules by means of the relative stiffnessσ measurements of the nodular components with the adjacent parenchyma, comparatively. It is a non-invasive and recent method able to contribute for differentiating benign thyroid nodules from malignant ones, particularly for nodules with suspicious US charecteristics, by using the relative stiffness measurement of the nodular component regarding the adjacent thyroid parenchyma [6].

In the present study, we examined and evaluated whether any association between the size of thyroid nodules of 10 mm and 15 mm, considered as the cut-off points, were emphasized by ATA management guideline 2015 [4], and the accuracy of three diagnostic tools for the thyroid malignancy: [1] thyroid strain elastography (SE), [2] TBSRTC for thyroid US-guided fine-needle aspiration (FNA), and [3] thyroid histopathology.

Methods

Study design and population

This was a retrospective study conducted at Giresun University Faculty of Medicine in Turkey. A retrospective archive study was designed by enrolling the documents, SE, one-surgeon performed US-guided-FNA, and histopathology results, of a sum of 425 cases with 500 thyroid nodules during February 2012 to April 2015. The eligible subjects were aged between 17 and 85 years with the thyroid nodules, diagnosed by clinical, imaging, and cytologic findings. During the study period, all the patients were subjected to standard imaging examinations with neck US (Figure 1A), Doppler US (Figure 1B), and SE (Figure 1C), followed by thyroid US-guided FNA cytology and histopathology according to ATA 2009 recommendations.

Inclusion criteria

The cases aged 17-85 years with thyroid nodules who were candidates for SE, US-guided FNA and thyroidectomy were suitable for the study enrollment.

Exclusion criteria

Any cases with thyroid nodule with purely cystic appearance, presence of cystic component 15%> of the nodule volume, large nodule (more than 85% of thyroid lobe volume) in order to have sufficient reference normal tissue and who had history of a previous non-thyroid carcinoma.

US-guided-FNA and FNA cytology

The cytologic samples were obtained under local anesthesia with Prilocaine hydrochloride, 400 mg/flacon for each targeted and indicated thyroid nodule as 3-8 smears by utilizing 27-gauge fine needle (Hayat, 2 ml 3P 27G, 0.40x50 mm, Istanbul, Turkey) by one-surgeon with >10 years of experience in the thyroid US-guided FNA and >17 years in the thyroid FNA. Currently, Moss et al [7] reported in a systematic review and meta-analysis that the needle biopsy of routine thyroid nodules should be performed with smaller needle gauges, 24-27 G, without aspiration. We performed all the US-guided FNA with the smallest needle, 27 G, like in our other studies [8,9]. The smear materials were prepared by air and alcohol fixation with an implementation into 95% alcohol and submitted to the Department of Pathology for the cytopathologic evaluation with haematoxylin-eosin (H&E), PAP, and May-Grünwald-Giemsa (MGG). The cytopathologic evaluations of the cases were performed based on TBSRTC, a six-tiered diagnostic system, as: [1] TBSRTC I, non-diagnostic; [2] TBSRTC II, benign; [3] TBSRTC III, AUS/FLUS; [4] TBSRTC IV, FN/SFN; [5] TBSRTC V, SM; [6] TBSRTC VI, malignant.

Neck ultrasound and strain elastography with Tsukuba Elasticity Score and concordant histopathologic features

B-mode neck US and SE were performed using Esaote MyLab 60, Geneva, Italy with 4-13 MHz broadbanded linear probe by one-surgeon with >10 years of experience in the thyroid US and SE imaging. A quasi-static strain imaging, SE, of axial and lateral tracking were characteristically implemented between each pair of radiofrequency (RF)-echo frames and the lateral displacements were discarded leaving a sequence of axial displacement images. Above the gray scale imaging, the imaging modality exhibited real time tissue elasticity images on-screen presentation for each compression-decompressin cycle with a color mapped translucent appearance. The elastograms were examined and subsequently evaluated by using a 5-point strain, TES, also known as Itoh-Score [10] or Elasto-Score, as: i) TES 1, Mostly green-coded lesions with equal elasticity with the surrounding tissue, Soft nodule (benign); ii) TES 2, Lesions with nonhomogeneous elasticity and blue-green areas, Soft nodule (benign); iii) TES 3, Lesions coded in blue in the center and green in the surrounding areas, Moderately hard (mostly benign); iv) TES 4, Completely blue lesions with no echogenic halo in the surrounding tissue, Hard nodule (malignant); v) TES 5, Completely

blue lesions with an echogenic halo in the surrounding tissue (loss of elasticity in the surrounding tissue), Hard nodule (malignant). On the basis of evaluation, TES 1 and 2 were evaluated as soft benign nodules, while the medium consistency, TES 3, was accepted as usually benign. However, TES 4 and 5 were reported as hard nodules and considered malignant [10,11].

Statistics

The data were presented descriptively. The statistical analysis were performed by using SPSS 23.0 computer program. The bar and boxplot graphs, frequency and crosstab tables were used to describe the variables in the analysis. Correlations between change in variables were analysed by carrying out x^2 independence hypothesis tests and McNemar tests and p value less than 0.05 was considered as statistically significant.

Results

A sum of 425 cases with 500 thyroid nodules were enrolled into the present study, including 329 (77.4%) women with mean age of 51.18 11.69 and 96 (22.6%) men with mean age of 51.81 14.27 years. The patients had undergone US-guided FNA during February 2012 to April 2015. Sonographically, TES 1, 2, 3, 4 (Figure 1C), and 5 were detected in 113 (22.6%), 242 (48.4%), 106 (21.2%), 28 (5.6%), 11 (2.2%), respectively for the cases with the undetermined cytology. Cytologically, TBSRTC I, II, III (Figure 1D), IV, V, and VI were detected as 45 (9.0%), 368 (73.6%), 49 (9.8%), 12 (2.4%), 19 (3.8%), and 7 (1.4%), respectively. Out of 500 thyroid nodules, 80 (16.0%) were under 10 mm while 420 (84.0%) were over 10 mm in diameter. Histopathologically, benign, 479 (95.8%); PTC, 14 (2.8%) (Figure 1E); FTC, 5 (1.0%); HCC, 2 (0.4%) were noticed. McNemar test was used to compare the thyroid nodules over 10 mm with TES 4 and 5 and no significant results were obtained (Table 1a,b) with an additional calculation of area under the curve (AUC) as 0.531 (Figure 2). The same condition existed for the thyroid nodules over 15 mm and TES 4 and 5 (Table 2) with

Table 1a. The numerical distribution of the both sides of cut-off 10 *vs.* TES

Nodule sizes	*TES*	
	1, 2, 3	*4, 5*
Under 10	76	4
Over 10	385	35

TES: Tsukuba Elasticity Score

Table 1b. The statistical analyses of the nodule size, cut-off 10 *vs.* TES 4 and 5

	Size, cut-off 10 vs. TES 4&5[a]
N	500
Chi-Square[b]	371,208
Asymp. Sig.	0,000

[a]McNemar test, [b]Continuity corrected, TES: Tsukuba Elasticity Score

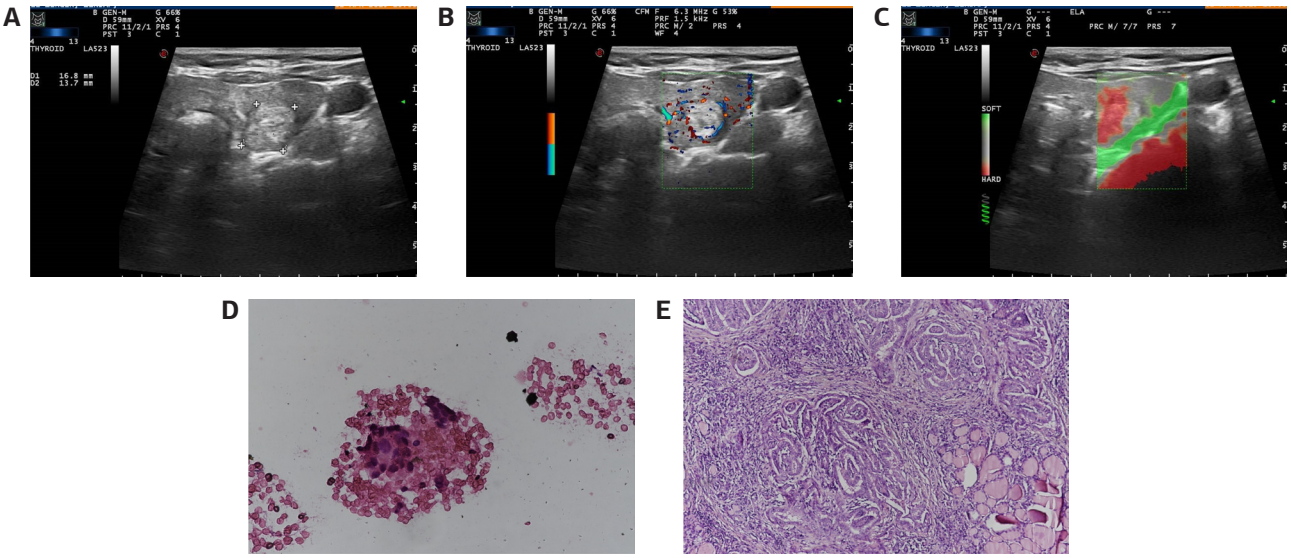

Figure 1. A: A sonographic photograph: an hyperechoic solid nodule, 16.8x13.7 mm, with micro- and macrocalcifications and irregular borders, at the thyroid left lobe dorsal zone, B-Mode US. US, Ultrasonography. **B:** A sonographic photograph: the peripheral and partial central vascularization in the nodule, depicted in Figure 1A, Doppler US. US, Ultrasonography. **C:** A sonographic photograph: TES 4 in the nodule in Figure 1A, depicted in Figure 1A, SE. TES: Tsukuba Elasticity Score; SE: Strain elastography. **D:** A photomicrograph revealing the cytopathology of TBRSTC III, (H&E; 20x0.40). TBSTRC: Thyroid Bethesda System for Reporting Thyroid Cytology; H & E: Hematoxylin & Eosin. **E:** A photomicrograph revealing the histopathology of PTC, (H&E; Original magnification, 40x0.10). PTC: Papillary Thyroid Carcinoma; H & E: Hematoxylin & Eosin.

an additional calculation of AUC as 0.623 (Figure 3). AUC for the nodules over 15 mm had higher value than the ones over 10 mm. Therefore, it may be asserted that the association between the higher nodule size and higher TES get strong as the cutt-off point was assigned as 15 mm. McNemar test was used to compare the thyroid nodules over 10 mm with TBSRTC III, IV, V, and VI, undetermined and malignant cytology, but no significance was detected (Table 3a, b) with an additional calculation of AUC as 0.517 (Figure 4). The same condition existed for the thyroid nodules over 15 mm and TBSRTC III, IV, V, and VI (Table 4a, b) with an additional calculation of AUC as 0.455 (Figure 5). AUC for the nodules over 15 mm had lower value than the ones over 10 mm. Therefore, it may be alleged that the association between nodule size and undetermined and malignant cytology weakens as the cutt-off point was assigned as 15 mm. McNemar test was used to compare the thyroid nodules over 10 mm with the malignant histopathology of thyroid, but no significance was reported (Table 5a, b) with an additional calculation of AUC as 0.509 (Figure 6). The same condition existed for the thyroid nodules

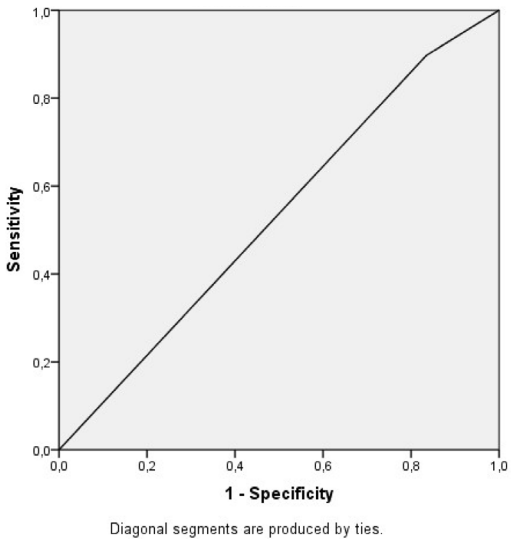

Figure 2. A standard ROC curve, sensitivity, specificity, and AUC of cut-off 10 *vs.* TES.

Table 2. The numerical distribution of the both sides of cut-off 15 *vs.* TES

Nodule size	*TES*	
	1, 2, 3	*4, 5*
Under 15	220	9
Over 15	241	30

TES: Tsukuba Elasticity Score

Table 3a. The numerical distribution of both sides of cut-off 10 *vs.* TBSRTC

Nodule sizes	*TBSRTC*	
	I, II	*III, IV, V, VI*
Under 10	69	11
Over 10	350	70

TES: Tsukuba Elasticity Score

Table 3b. The statistical analyses of the nodule size, cut-off 10 *vs.* TBSRTC

	Size, cut-off 10 vs. TBSRTC[a]
N	500
Chi-square[b]	316,465
Asymp. Sig.	0.000

[a]McNemar test, [b]Continuity corrected, TES: Tsukuba Elasticity Score

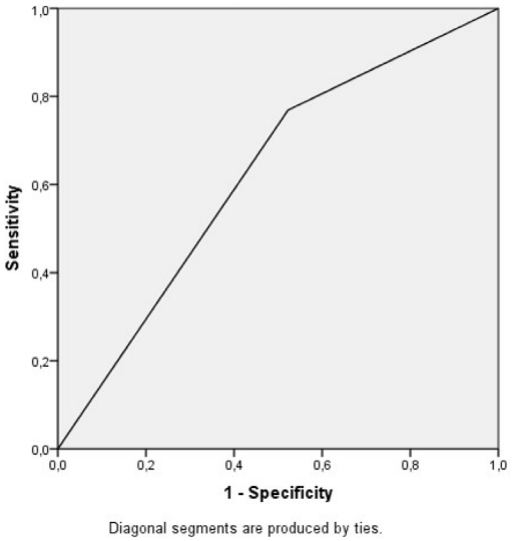

Figure 3. A standard ROC curve, sensitivity, specificity, and AUC of cut-off 15 *vs.* TES.

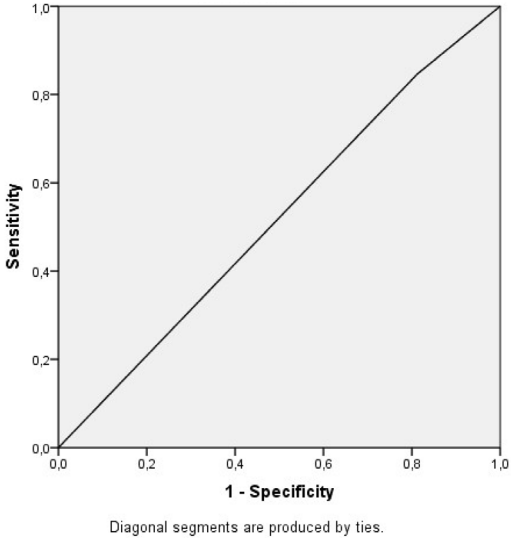

Figure 4. A standard ROC curve, sensitivity, specificity, and AUC of cut-off 10 *vs.* TBSRTC.

Table 4a. The numerical distribution of the both sides of cut-off 15 *vs.* TBSRTC

Nodule size	*TBSRTC*	
	I, II	*III, IV, V, VI*
Under 15	202	27
Over 15	217	54

TES: Tsukuba Elasticity Score

Table 4b. The statistical analyses of the nodule size, cut-off 15 *vs.* TBSRTC

	Size, cut-off 15 vs. TBSRTC[a]
N	500
Chi-square[b]	146,398
Asymp. Sig.	0.000

[a]McNemar test, [b]Continuity corrected, TES: Tsukuba Elasticity Score

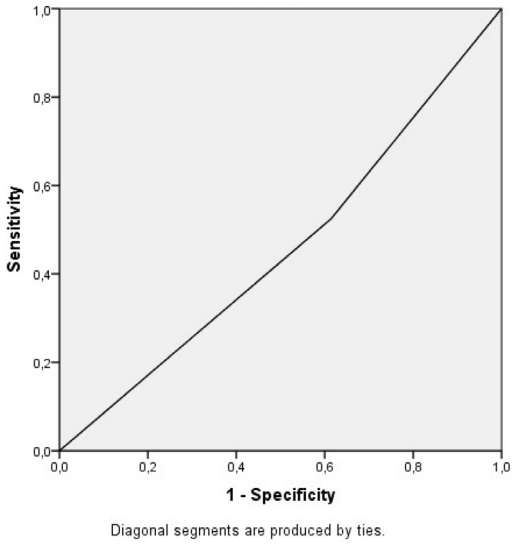

Figure 5. A standard ROC curve, sensitivity, specificity, and AUC of cut-off 15 *vs.* TBSRTC.

Table 5a. The numerical distribution of the both sides of cut-off 10 *vs.* histopathology

Nodule size	*Histopathology*	
	Benign	*Malignant*
Under 10	77	3
Over 10	402	18

TES: Tsukuba Elasticity Score

Table 5b. Statistical analyses of the nodule size, cut-off 10 *vs.* histopathology

	Size, cut-off 10 vs. histopathology[a]
N	500
Chi-square[b]	391,121
Asymp. Sig.	0.000

[a]McNemar test, [b]Continuity corrected, TES: Tsukuba Elasticity Score

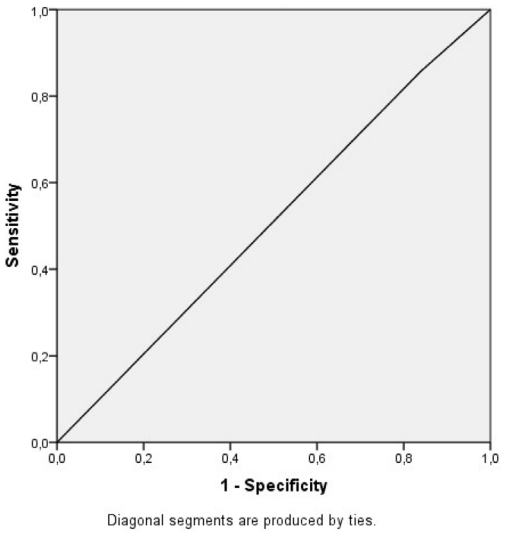

Figure 6. A standard ROC curve, sensitivity, specificity, and AUC of cut-off 10 *vs.* Histopathology.

Table 6a. The numerical distribution of the both sides of cut-off 15 *vs.* histopathology

Nodule size	*Histopathology*	
	Benign	*Malignant*
Under 15	220	9
Over 15	259	12

TES: Tsukuba Elasticity Score

Table 6b. The statistical analyses of the nodule size, cut-off 15 *vs.* histopathology

	Size, cut-off 15 vs. histopathologya
N	500
Chi-square[b]	231,347
Asymp. Sig.	0.000

[a]McNemar test, [b]Continuity corrected, TES: Tsukuba Elasticity Score

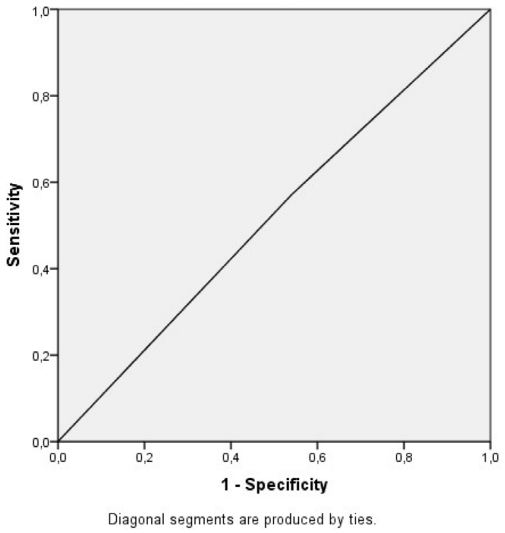

Figure 7. A standard ROC curve, sensitivity, specificity, and AUC of cut-off 15 *vs.* Histopathology.

over 15 mm and malignant histopathology (Table 6a, b) with an additional calculation of AUC as 0.515 (Figure 7). AUC for the nodules over 15 mm was higher than the ones over 10 mm. Hence, it may be concluded that the association between nodule size and the malignant histopathology gain strength as the cutt-off point was assigned as 15 mm.

Discussion

Management of a patient with a nodular thyroid disease is still an essential and crucial issue of thyroidology and some notable guidelines such as ATA [3,4], the American Association of Clinical Endocrinologists (AACE)/Asociazione Medici Endocrinologi (Italian Association of Clinical Endocrinologists) (AME), the European Thyroid Association (ETA) [12], and the Society of Radiologists in Ultrasound (SRU are important) [13]. ATA managements guidelines in 2015 declared FNA was still being the most accurate and cost-effective method for evaluating the thyroid nodules (recommendation 7). This last ATA guideline offers prolongation and maintenance for utilization of TBSRTC, provided concensus recommendations of the 2007 NCI Thyroid Fine-Needle Aspiration State of the Science Conference, should report the thyroid nodule FNA cytology (recommendation 9) [4].

This present single-center study retrospectively determined the thyroid nodule size, 10 and 15 mm in diameter, in SE, categories of TBSRTC for US-guided FNA, and the results of histopathology of indicated thyroidectomies. Some recommendations on the size selection criteria for US-guided FNA for the thyroid nodules have been set at a cut-off value of 10 mm [14,15]. AACE/AME recommended FNA for the nodules with diameter larger than 10 mm that are solid and hypoechoic on US (Grade B; BEL [best evidence level] 3) [16]. ETA came together with the international experts in a panel to establish the European guidelines on US risk stratification of thyroid nodules. The mentioned panel produced the novel European Thyroid Imaging and Reporting Data System (EU-TIRADS) based on a review of the literature and on the AACE, ATA, and Korean guidelines, comprising a thyroid US lexicon. This was a kind of a standardized report, comprising the definitions of benign and low-, intermediate-, and high-risk nodules, with their estimated risks of malignancy in each category and the related indications for FNA [16,17]. SRU recommended to strongly considering US-guided FNA for the thyroid nodules ≥10 mm in largest diameter with microcalcifications, ≥15 mm in largest diameter with i) solid or almost entirely solid or ii) coarse calcifications within the nodule. SRU recommended considering US-guided FNA for the thyroid nodules ≥20 mm in largest diameter with i) mixed solid and cystic or ii) almost entirely cystic with a solid mural component or the nodule has shown substantial growth since prior US examination [13]. ATA managements guidelines in 2009 recommended FNA for the nodules ≥10 mm with microcalcifications (Recommendation B) and solid hypoechoic nodules >10 mm (Recommendation B) with solid iso- hyperechoic nodules ≥10-15 mm (Recommendation C) [3]. ATA managements guidelines (2015) for adult patients with thyroid nodules and differentiated thyroid cancer [18] also recommended that nodules ≥10 mm with high to intermediate suspicion sonographic pattern, ≥15 mm with low suspicion pattern, and ≥20 mm with very low suspicioun pattern (e.g. spongiform) (Recommendation 8, IID) should be evaluated by US-guided FNA. Since 1923 ATA has a long history of generating clinical practice guidelines and statements with global impact on an ongoing basis in terms of clinical management, education, and research in thyroid diseases [19]. It is also stated that if none of the nodules has a high or moderate suspicion sonographic pattern, and multiple sonographically similar very low or low suspicion pattern nodules coalesce with no intervening normal parenchyma, the likelihood of malignancy is low and it is reasonable to aspirate the largest nodules (≥2 cm) or continue surveillance without FNA (Recommendation 21, C) [4]. Besides, 20 mm is designated as the cut-off point between T1b and T2 in AJCC 7th edition/TNM classification system for DTC [20]. A German study with 500 cases of PTC and follicular thyroid carcinoma (FTC) by Machens et al [21] reported that the primary thyroid tumors did not progress to distant metastasis until they were over 20 mm in the greatest diameter. They proposed critical threshold diameter 20 mm, as being useful in stratifying the thyroid nodules based on the risk of distant metastasis in DTC.

It is obviously recognized that the thyroid nodule size, particularly 10, 15, and 20 mm as the cut-off points, has been emphasized in various studies and importantly in the guidelines, evaluating the thyroid nodules and thyroid cancer, to date, momentously. Therefore, we intended to concern this crucial topic with interest and respect by annexing the effect of SE to the mentioned subject. First of all, we investigated whether there exists any association for distinguishing malignant from benign thyroid nodules in terms of the nodule size over 20 or under 20 mm. We retrospectively analysed the records of 82 thyroid nodules with undetermined cytology among 547 consecutive eligible patients with 655 thyroid nodules from April 2012 to April 2016. The outcomes of our 4-year single-centre experience,

USs, SEs, and US-guided FNAs of the cases visualized and performed by one-surgeon, were: no significance was revealed on the basis of the nodules over 20 mm, regarding: i) TES 4 and 5, ii) undetermined cytology, and iii) malignant histopathology [9]. Secondly, in the present study, we proposed to study 10 and 15 mm as the cut-off points and observed the efficacy on the crucial markers of three diagnostic tools; SE, US-guided FNA cytology, and histopathology. Our new outcomes based on these markers were as follows: no significance was revealed on the basis of the nodules both over 10 mm and over 15 mm, regarding: i) TES 4 and 5 with AUC 0.531 for cut-off 10 and 0.623 for 15, ii) undetermined and malignant cytology (TBSRTC III, IV, V, and VI) with AUC 0.517 for cut-off 10 and 0.455 for 15; and iii) malignant histopathology with AUC 0.509 for cut-off 10 and 0.515 for 15. AUC of TES 4 and 5 for 15 was higher than 10. Therefore, it may be alleged that the correlation between the nodule size and TES 4 and 5 gets stronger as the cuttoff was designated as 15 mm. AUC of TBSRTC III, IV, V, and VI for 15 was lower than 10. Hence, it may be asserted the relationship between the nodule size and undetermined and malignant cytology gets weaker as the cuttoff was defined as 15 mm. AUC of malignant histopathology for 15 was higher than 10. Thereby, it may be adopted that the association between nodule size and the malignant histopathology gets stronger as the cuttoff was appointed as 15 mm.

Limitations

Our study was a single-center retrospective study. We had studied both undetermined, TBSRTC III, IV, and V, and malignant, TBSRTC VI, cytology, instead of working with two mentioned problematic cytologic group, separetely. We also had not studied the non-diagnostic group of cytology, TBSRTC I. Follicular variant of papillary thyroid carcinoma (FVPTC) is known as an aggressive variant of PTC [22-24]. A recent nomenclature revision was accepted at a face-to-face conference in The Endocrine Pathology Society Conference, Boston, Massachusetts, March 20-21, 2015. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was accepted and replaced what was previously known as non-invasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC). NIFTP has been declared to exhibit benign/indolent clinical behaviour compared with invasive follicular variant of papillary thyroid carcinoma (FVPTC), so this thyroid tumor was downgraded from cancer to noninvasive follicular thyroid neoplasm. However, surgical approach is still the treatment of choice for this group despite the mentioned alteration in nomenclature. This recommendation was published in August 2016 and the present retrospective study had not been performed on the basis of this new terminology [25].

Conclusions

Outcomes of the present 3-year single-center study revealed that the designation of 10 and 15 mm as the cut-off points may not be a role in estimating the thyroid malignancy in terms of three diagnostic tools: SE, US-guided FNA cytology, and histopathology. However, higher cut-off, 15 mm, may strengthen the association with TES 4 and 5 and malignant histopathology while weaken it with TBSRTC III, IV, V, and VI, comparing the lower one, 10 mm. To our knowledge, it is the first study in the English language literature, investigating the specific size cut-offs of 10 and 15 mm whether effective on predicting the thyroid malignancy combined with strain elastography, cytology, TBSRTC, and histopathology.

Additionally, in our experience of own previous study, the nodule size of 20 mm in diameter, had also not a distinct 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 [9].

Authors' contribution

IS and DS contributed in constituting the notion, hypothesis, intellectual planning and management of the study as well as writing the whole manuscript with the linguistic and academic revisions. IS also contributed in examining each patient in the outpatient clinic and visualizing and performing US, SE, and US-guided-FNA for the thyroid nodules. EE and DS performed the statistical analysis in a detail. DS, TO, IA TK, SV, and TB collected and analysed the data. AT wrote some parts of the radiologic evaluations. All the authors finally approved the submitted and proofread version.

Acknowledgements for research support

We would like to thank the residents and students of Department of General Surgery and all the staff and personnel of Department of Pathology, General Surgery, and Radiology, at Giresun University-Ministry of Health Prof. Dr. A. Ilhan Ozdemir Education and Research Hospital, Giresun, Turkey.

Conflict of interests

The authors declare no conflict of interests.

References

1. Bardet S, Ciappuccini R, Pellot-Barakat C et al. Shear Wave Elastography in Thyroid Nodules with Indeterminate Cytology: Results of a Prospective Bicentric Study. Thyroid 2017;27:1441-9.
2. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Thyroid 2009;19:1159-65.
3. The American Thyroid Association Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-1214.
4. Haugen BR, Alexander EK, Bible KC 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.
5. Ophir J, Céspedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. Ultrason Imaging 1991;13:111-3.
6. Garra BS. Elastography: current status, future prospects, and making it work for you. Ultrasound Q 2011;27:177-86.
7. Moss WJ, Finegersh A, Pang J et al. Needle Biopsy of Routine Thyroid Nodules Should Be Performed Using a Capillary Action Technique with 24- to 27-Gauge Needles: A Systematic Review and Meta-Analysis. Thyroid 2018;28:857-63.
8. Sengul D, Sengul I, Van Slycke S. Risk stratification of the thyroid nodule with Bethesda indeterminate cytology, category III, IV, V on the one surgeon-performed US-guided fine-needle aspiration with 27-gauge needle, verified by histopathology of thyroidectomy: The additional value of one surgeon-performed elastography. Acta Chir Belg 2019;119:38-46.
9. Sengul D, Sengul I. Association between Tsukuba Elasticity Score 4 and 5 on elastography and Bethesda indeterminate cytology on US-guided FNA with 27-G needle, verified by histopathology: As a cutt of point of 20 mm in a size of diameter, designated for the thyroid nodules. JBUON 2019;24:382-90.
10. Itoh A, Ueno E, Tohno E et al. Breast disease: clinical application of US elastography for diagnosis. Radiology 2006;239:341-50.
11. Hong Y, Liu X, Li Z, Zhang X, Chen M, Luo Z. Real-time ultrasound elastography in the differential diagnosis of benign and malignant thyroid nodules. J Ultrasound Med 2009;28:861-7.
12. Gharib H, Papini E, Paschke R et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi and European Thyroid Association Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. Endocr Pract 2010;16:468-75.
13. Frates MC, Benson CB, Charboneau JW et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005;237:794-800.
14. Ucler R, Usluogullari CA, Tam AA et al. The diagnostic accuracy of ultrasound-guided fine-needle aspiration biopsy for thyroid nodules three centimeters or larger in size. Diagn Cytopathol 2015;43:622-8.
15. Yang GC, Livolsi VA, Baloch ZW. Thyroid microcarcinoma: fine-needle aspiration diagnosis and histologic follow-up. Int J Surg Pathol 2002;10:133-9.
16. Gharib H, Papini E, Paschke R et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: Executive Summary of recommendations. J Endocrinol Invest 2010;33:287-91.
17. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. Eur Thyroid J 2017;6:225-37.
18. Sengul D, Sengul I. Are there any variation in neutrophil lymphocyte ratio, mean platelet volume, and platelet count between papillary thyroid cancer and benign nodular thyroid diseases ? Sanamed 2018;13:11-6.
19. Sawka AM, Carty SE, Haugen BR, et al. American Thyroid Association Guidelines and Statements: Past, Present, and Future. Thyroid 2018;28:707-21.
20. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. Thyroid cancer staging. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (Eds): AJCC Cancer Staging Handbook (7th Edn). Springer-Verlag, New York, NY, 2010, pp 59-64.
21. Machens A, Holzhausen HJ, Dralle H. The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. Cancer 2005;103:2269-73.
22. Deligiorgi MV, Mahaira H, Eftychiadis C, et al. RANKL, OPG, TRAIL, KRas, and c-Fos expression in relation to central lymph node metastases in papillary thyroid carcinoma. JBUON 2018;23:1029-40.
23. Markovic I, Goran M, Besic N et al. Multifocality as independent prognostic factor in papillary thyroid cancer - A multivariate analysis. J BUON 2018;23:1049-1054.
24. Sayiner A, Suren D. Expression of human telomerase reverse transcriptase (hTERT) in thyroid neoplasms. JBUON 2018;23:229-33.
25. Nikiforov YE, Seethala RR, Tallini G et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016;2:1023-29.