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ORIGINAL ARTICLE

Laterality of the thyroid nodules, anatomic and sonographic, as an estimator of thyroid malignancy and its neoplastic nature by comparing the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) and histopathology

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Summary

Purpose: *To assess the association between the topographic and sonographic laterality of the thyroid nodules and the malignancy for those who had undergone ultrasonography (US)-guided fine-needle aspiration (FNA) (US-FNA) and following relevant indicated thyroidectomy.*

Methods: *A retrospective analysis from April 2011 to October 2015 was conducted by enrolling the documents of 501 consecutive eligible patients with 601 thyroid nodules who had undergone neck US, Doppler US, and US-FNA. The prediction of malignancy by means of laterality of 95 thyroid nodules with undetermined cytology on the basis of the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was evaluated histopathologically with comparison of three locations, separately.*

Results: *Six hundred and one nodules in 501 cases were studied and 249 nodules (49.8%) were topographically located at the right lobe (Location 1/Loc1), while 255 (42.4%) at the left lobe (Location 2/Loc2), 46 (7.7%) at the isthmus (Location 3/Loc3), and 1 (0.2%) was an accessory thyroid gland (Location 4/Loc4). Three different comparisons were performed regarding the locations, which revealed that the specificity did not change regarding the locations while the sensitivity of Loc3 was higher than that of Loc1 and Loc2.*

Conclusions: *The preliminary data of 4.5-year single-center study proved that the isthmus location may be more beneficial to estimate the malignancy on the basis of toposonographic laterality of the nodules with undetermined cytology. This notewothy outcome may be considered particularly for the challenging cases with undetermined cytology in Endocrine Surgery and Thyroidology.*

Key words: *laterality, fine-needle aspiration, Bethesda thyroid, TBSRTC, undetermined cytology, thyroidectomy, thyroidology, ultrasonography*

Introduction

Fine needle aspiration (FNA) is the standard tool for distinguishing the thyroid nodules in order to decide surgical intervention or clinical follow-up [1-8]. Nevertheless, indeterminate cytology can be as high as 5-20% [9,10]. Since its inception, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) established a standardized reporting system with a six-tiered categories for thyroid FNA specimens, as follows: (1) non-diagnostic, Category I; (2) benign, II; (3) atypia of undetermined signifi-

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cance or follicular lesion of undetermined significance (AUS/FLUS), III; (4) follicular neoplasm or suspicious for a follicular neoplasm FN/SFN IV; (5) suspicious for malignancy (SM), V; and (6) malignant, VI. Using TBSRTC, cytopathologists can communicate their interpretations to the referring physician [11]. TBSRTC has been widely adopted in many countries and has been endorsed by the American Thyroid Association (ATA) management guidelines [12,13].

The purpose of the present study was to investigate the association between the sonographic laterality of the thyroid nodules with undetermined cytology and their malignancies.

Methods

Study design and population

A retrospective analysis was carried out by collecting and studying the documents of the cases with thyroid nodules and FNA cytology (FNAC) between April 2011 and October 2015. All the cases had undergone neck US and Doppler US to clarify whether they had malignant US characteristics. Each indicated thyroid nodule, acccording to 2009 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [14], had ungergone US-FNA which had performed by one surgeon (IS) to rule out malignant formations in the thyroid nodules. Any correlation between the sonographic laterality and malignancy for the nodules with undetermined cytology was intended to comparatively ascertain histopathologic interrelation.

US-guided FNA and FNA cytology

From each targeted and indicated thyroid nodule, 3-8 smears were obtained via 27-gauge fine needle (Hayat, 2 ml 3P 27G, 0.40x50 mm, Istanbul, Turkey) under local anesthesia with prilocaine hydrochloride, 400 mg/flacon. In July 2018, Moss et al [14] reported that the needle biopsy of routine thyroid nodules should be performed with smaller needle gauges (24-27 G). In the present study, all the US-FNA were performed with the smallest needle used ever (27 G). The smear materials were air-dried and fixed with 95% alcohol and microscopically evaluated by using haematoxylin-eosin (H&E), PAP, and May-Grünwald-Giemsa (MGG) stains. All the cases were evaluated cytopathologically according to TBSRTC, a six-tiered diagnostic system.

Neck sonography

Neck US and Doppler US were performed using Esaote MyLab 60, Genova, Italy with 4-13 MHz broadband linear probe with mean broadband of 12 MHz. All the thyroid nodules were examined meticulously by neck and Doppler US during 4.5 years.

Inclusion and exclusion criteria

The present study enrollment included cases aged 17-85 years with thyroid nodules who were candidates for US-FNA application according to 2009 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [12], while the exclusion criteria were the thyroid nodules that had not undergone US-FNA and the purely cystic nodules.

Statistics

The statistical analyses were performed using SPSS 23.0 and NCSS 12.0 computer programs. Descriptive statistics and frequency tables were created to examine the variables in the analysis. ROC curves were plotted to visualize the diagnostic powers of the methods. The statistical parameters, area under the curve (AUC), specificity and sensitivity, were computed for each diagnostic method. Moreover, Z-tests were used to compare AUC statistics and the Chi-square (x^2) test was applied to compare the statistical values of sensitivity and specificity. The statistically 2-sided prob level <0.01 in Z-test was performed for AUC. For all the null hypothesis tests, one-sided or two-sided probability levels or significance levels (according to the null hypothesis (H_0) were computed and given in the related Tables.

Results

A sum of 501 cases (389; 77.6% women and 112; 22.4% men) with 601 thyroid nodules which had undergone US-FNA were enrolled. The mean age of the patients was 51.63±12.64 years (17-85), and the mean size of the largest diameter was 18.70±9.42 mm (4-56). Toposonographically, 249 nodules (49.8%) were located at the right lobe

Table 1. Sensitivity, specificity, PPV, NPV, likelihood ratio, AUC, empirical ROC curve of the Loc1, right lobe

Predictive value section for C2 (histopathology) using the empirical ROC curve, Loc1					
TBSRTC cut-off value	*Sensitivity*	*Specificity*	*Likelihood ratio*	*PPV*	*NPV*
2.00 (III, IV, V)	0.92308	0.86364	6.76923	0.23529	0.99597
Empirical area under the curve analysis for condition= C2 (histopathology)					
Criterion	*Empirical estimate of AUC*	*AUC's standard error*	*Z-value to test AUC>0.5*	*1-sided prob level*	*2-sided prob level*
TBSRTC	0.89336	0.03978	9.89	0.0000	0.0000

For abbreviations see text

(Loc1), 255 (42.4%) at the left lobe (Loc2), 46 (7.7%) at the isthmus (Loc3), and 1 (0.2%) was an accessory gland (Loc4) (Table 1). Cytolopathologically (Table 1), TBSRTC I, II, III, IV, V, and VI were detected in 21 (3.5%), 484 (80.5%) (Figure 1), 60 (10.0%), 15 (2.5%) (Figure 2), 20 (3.3%) and 1 (0.2%), respectively. Undetermined cytology had 95 (15.8%) patients, while benign ones had 484 (80.5%). Histopathologically (Table 1), benign papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hurthle cell carcinoma (HCC) were detected in 577 (96.00%) (Figure 2), 17 (2.83%), 5 (0.84%), and 2 (0.33%) cases, respectively. The relationship betweeen TBSRTC III, IV, and V, undetermined cytology, and histopathology were also analysed for each location confronting with the benign cytology, TBSRTC II. TBSRTC was determined as an useful diagnostic test, in terms of the comparison between undetermined and benign cytologies, to estimate their histopathology for all three locations: right lobe (Table 1, Figure 3), left lobe (Table 2, Figure 4), and istmus (Table 3, Figure 5). In addition, three different comparisons regarding the locations revealed that the specificity did not change concerning the locations while the sensitivity of Loc3 was higher than the ones for Loc1 and Loc2 (Tables 4-6).

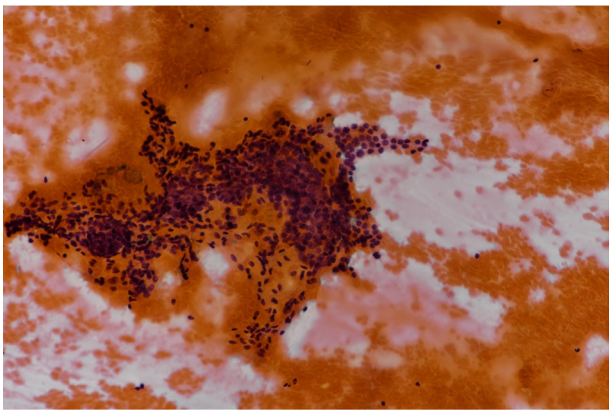

Figure 1. A photomicrograph revealing the cytopathology of TBRSTC, category III (PAP; original magnification, 20×0.40).

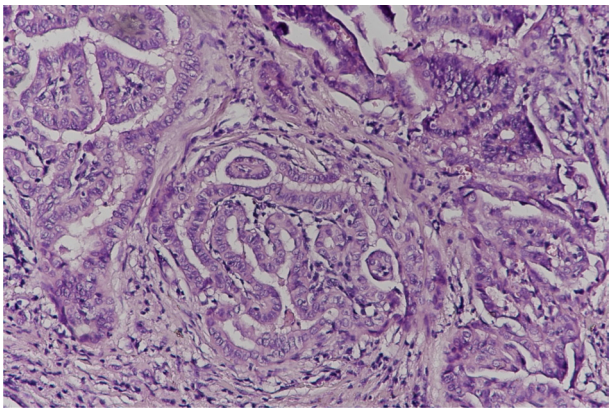

Figure 2. A photomicrograph revealing the histopathology (PTC H&E; Original magnification, 40×0.75).

Table 2. Sensitivity, specificity, PPV, NPV, likelihood ratio, AUC, empirical ROC curve of the Loc2, left lobe

Predictive value section for C4 (histopathology) using the empirical ROC curve, Loc2					
TBSRTC cut-off value	*Sensitivity*	*Specificity*	*Likelihood ratio*	*PPV*	*NPV*
2.00 (III, IV, V)	0.87500	0.90283	9.00521	0.22581	0.99554
Empirical area under the curve analysis for condition= C4 (histopathology)					
Criterion	*Empirical estimate of AUC*	*AUC's standard error*	*Z-value to test AUC>0.5*	*1-sided prob level*	*2-sided prob level*
TBSRTC	0.88892	0.06321	6.15	0.0000	0.0000

For abbreviations see text

Table 3. Sensitivity, specificity, PPV, NPV, likelihood ratio, AUC, empirical ROC curve of the Loc3, isthmus

Predictive value section for C6 (histopathology) using the empirical ROC curve, Loc3					
TBSRTC cut-off value	*Sensitivity*	*Specificity*	*Likelihood ratio*	*PPV*	*NPV*
2.00 (III, IV, V)	1.0000	0.74419	3.90909	0.21429	1.0000
Empirical area under the curve analysis for condition= C6 (histopathology)					
Criterion	*Empirical estimate of AUC*	*AUC's standard error*	*Z-value to test AUC>0.5*	*1-sided prob level*	*2-sided prob level*
TBSRTC	0.87209	0.03366	11.05	0.0000	0.0000

For abbreviations see text

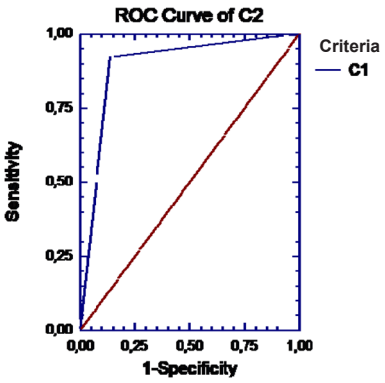

Figure 3. Sensitivity, specificity, PPV, NPV, AUC, and ROC curve of the Loc1. C1: TBSRTC of Loc1, Right lobe, C2: Histopathology of Loc1, Right lobe

Discussion

A widely used diagnostic cytopathologic method for suspicious thyroid nodules, TBSRTC, was set up in 2007 by the National Cancer Institute (NCI), Thyroid Fine Needle Aspiration State of the Art and Science Conference, held in Bethesda, Maryland, standardizing the reporting of thyroid cytopathology. Six diagnostic categories in the mentioned system, established through a multidisciplinary formulation, were linked to certain ranges of malignancy risk and clinical management guidelines [12]. The recent term of "non-invasive follicular thyroid neoplasm with papillary-like nuclear fea-

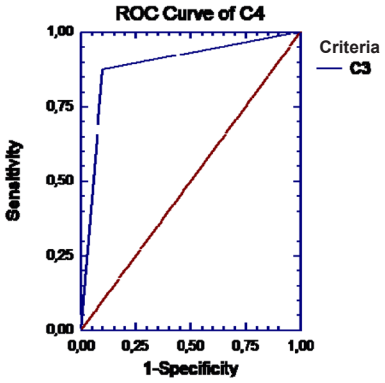

Figure 4. Sensitivity, specificity, PPV, NPV, AUC, and ROC curve of the Loc2. C3: TBSRTC of Loc2, Left lobe, C4: Histopathology of Loc2, Left lobe

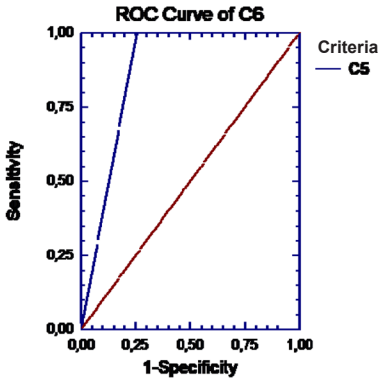

Figure 5. Sensitivity, specificity, PPV, NPV, AUC, and ROC curve of the Loc3. C5: TBSRTC of Loc3, Isthmus, C6: Histopathology of Loc3, Isthmus

Table 4. Comparison of Loc1 vs Loc2 with NCSS 12.0

Sensitivity and specificity Hypothesis Test Section				
Null Hypothesis (Equality, Se/Sp)	*Value*	*Chi-square*	*Prob level*	*Decision at 5.0% Level*
Se1= Se2	-0,0392	1,9538	0,1622	Cannot Reject H0
Sp1= Sp2	0,0481	0,1328	0,7155	Cannot Reject H0

Loc1: Location 1 (right lobe); Loc2: Location 2 (left lobe); Se: sensitivity; Sp: specificity; H0: Null Hypothesis, Equality of Se/Sp for Loc 1 vs. Loc 2

Table 5. Comparison of Loc1 vs Loc3 with NCSS 12.0

Null Hypothesis (Equality, Se/Sp)	*Value*	*Chi-square*	*Prob level*	*Decision at 5.0% Level*
Se1= Se3	0.1195	4.1384	0.0419	Reject H0
Sp1= Sp3	-0.0769	0.2462	0.6198	Cannot Reject H0

Loc1: Location 1 (right lobe); Loc3: Location 3 (isthmus); Se: sensitivity; Sp: specificity; H0: Null Hypothesis, Equality of Se/Sp for Loc 1 vs. Loc 3

Table 6. Comparison of Loc2 vs Loc3 with NCSS 12.0

Null Hypothesis (Equality, Se/Sp)	*Value*	*Chi-square*	*Prob level*	*Decision at 5.0% Level*
Se2= Se3	0.1586	8.6861	0.0032	Reject H0
Sp2= Sp3	-0.1250	0.4125	0.5207	Cannot Reject H0

Loc 2: Location 2 (left lobe); Loc3: Location 3 (isthmus); Se: sensitivity; Sp: specificity; H0: Null Hypothesis, Equality of Se/Sp for Loc 2 vs. Loc 3

tures (NIFTP)" replaced the previous term "non-invasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC)" at the Endocrine Pathology Society Conference, in Boston, Massachusetts, March 20-21, 2015 [15].

Moreover, Ali and Vielh expressed their opinion at the 19th International Congress of Cytology (ICC) in Pacifico Yokohama, Japan in 28 May-June 01, 2016, proposing the modifications and updates for the second edition, TBSRTC 2nd [16,17]. TBSRTC 2nd has revealed no real change in main terminology, concerning the 1st edition. Recently, Cibas and Ali [18] reported 'The 2017 Bethesda System for reporting thyroid cytopathology', proposing the utilization 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. The 2017 revision was inspired by new data and new developments in the field of thyroid pathology and thyroidology. It revised the guidelines for the management of patients with thyroid nodules, the introduction of molecular testing as an adjunct to cytopathologic examination, and the reclassification of the NIFTP.

However, in terms of cytologic approach in view of NIFTP, some options have put forward revised risk of malignancy (ROM), new ATA management guidelines for the thyroid nodule and cancer, and other aspects, in particular, the molecular ones [19]. Very recently, in October 2018, Mao et al [20] reported on their interesting final pathology that NIFTP should be regarded as an indolent tumor requiring no further surgical treatment.

Very recently, on March 2020, Zajkowska et al [21] reported that although these tumours can be effectively treated by lobectomy, total thyroidectomy remains an option for some patients, in particular for those who do not accept the requirement for the follow-up of remaining thyroid lobe and the risk of a possible redo surgery. Radioactive iodine (RAI) ablation and thyroid stimulating hormone suppression therapy are not required. NIFTP has an extremely good prognosis, but it cannot be considered as a benign lesion. Additionally, regional cervical lymph node and distant metastases are low but not negligible for the mentioned entity.

Zhang et al [22] presented a study entitled "thyroid nodule location on ultrasonography as a predictor of malignancy" at the 27th American Association of Clinical Endocrinologists (AACE) meeting, which was held in Boston, MA, May 16-20, 2018 as a late-breaking abstract. In that study Zhang et al were the first to demonstrate whether an association existed between the thyroid nodule location and the likelihood of thyroid nodule malignancy. Zhang's group [24] published a retrospective study for the thyroid nodules from 188 patients who had undergone FNA in terms of the laterality of the nodules (left vs isthmus vs right). They reported that the thyroid nodules were evenly distributed between the left and right lobes (50.5% vs 47.3%), with only 2.1% located in the isthmus. In our study, we similarly detected more nodules at the right lobe (49.8%) than the left (42.4%), with 7.7% located at the isthmus. Zhang et al [22] did not report any significant difference between the thyroid nodules and the thyroid malignancy in terms of laterality. In the present study, it was also investigated whether the TBSRTC 1st predicted the malignant histopathology of the thyroid nodules on the basis of their topography (right lobe, left lobe, and isthmus) and the topographic outcomes were found to be significant. Zhang et al [22,23] studied both the laterality and polarity of the nodules for predicting malignancy. To our knowledge, this is the first study in the English literature to investigate solely the efficacy of the laterality of the nodules as a toposonographic anatomic feature, forecasting the thyroid malignancy.

Conclusions

In conclusion, TBSRTC was useful to anticipate the histopathology on the basis of matching undetermined and benign cytology for all the three locations. In addition, the specificity did not differ regarding the locations, while the sensitivity for Loc3 and isthmus, was higher than the the others. The isthmus location may be more beneficial comparing the other locations in terms of predicting malignancy on the basis of anatomosonographic laterality of the nodules. This remarkable outcome of the present study may be considered particularly for the challenging cases with undetermined cytology in thyroidology. To our knowledge, the present study for which we hope to be able to contribute to Endocrine Surgery and Thyroidology, is the first study in the English literature, investigating the possible association of the malignancy and solely toposonographic laterality of the thyroid nodules with undetermined cytology in a largest serial before.

Authors'contribution

IS and DS contributed in the constituting the notion and null hypothesis, intellectual planning and management of the study, writing the whole manuscript, and its linguistic and academic revisions. Besides, DS and TO contributed in the collection of the data, while EE and DS in performing the statistical analyses. IS contributed in examining all the patients and performing US-FNA for each

indicated thyroid nodule. All the authors finally approved the submitted and proof versions without any conflict of interest.

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Conflict of interests

The authors declare no conflict of interests.

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