A Comparison of Two Widely Used Risk Stratification Systems for Thyroid Nodule Sonographic Evaluation

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ABSTRACT **Background:** The 2015 American Thyroid Association (ATA2015) and the American College of Radiology Thyroid Imaging and Reporting Data System (ACR TI-RADS) are two widely used thyroid sonographic systems.

Objectives: To compare the two systems for accuracy of cancer risk prediction.

Methods: Preoperative ultrasound images from 265 patients who underwent thyroidectomy at our hospital from January 2012 to March 2019 were retrospectively categorized by the ACR TI-RADS and ATA2015 systems. Diagnostic performances were compared.

Results: Of 238 nodules assessed, 115 were malignant. Malignancy risks for the five ACR TI-RADS categories were 0%, 7.5%, 11.4%, 59.6%, and 90.0%. Malignancy risks for the five ATA2015 categories were 0%, 6.8%, 17.0%, 55.5%, and 92.1%. The proportion of total nodules biopsied was higher with the ATA2015 system than the ACR TI-RADS system: 88.7% vs. 66.3%. Proportions of malignant nodules and benign nodules biopsied were higher with ATA2015 than with ACR TI-RADS: 93.3% vs. 87.8% and 84.4% vs. 46.3%, respectively. Specificity and sensitivity rates were 53.6% and 84.3%, respectively, for ACR TI-RADS, and 15.5% and 93.3%, respectively, for ATA2015. The two systems showed similarly accurate diagnostic performance (AUC > 0.88). False negative rates for ACR TI-RADS and ATA2015 were 15.6% and 6.6%, respectively. Rates of missed aggressive cancer were similar for the two systems: 3.4% and 3.7%, respectively.

Conclusion: ACR TI-RADS was superior to ATA2015 in specificity and avoiding unnecessary biopsies. ATA2015 yielded better sensitivity and a lower false negative rate. Identification of aggressive cancers was identical in the two systems.

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Thyroid nodules are common, with an ultrasound detection rate of 20–30% in the general population [1]. Since only 7–15% of them are malignant, and often exhibit very indolent behavior, only a small percentage of nodules need to be biopsied [2,3]. The current clinical approach regarding the need to perform fine needle aspiration (FNA) biopsy is based on sonographic findings of the suspected thyroid nodule [4]. Certain ultrasound characteristics are well-established as predictors of malignancy: calcifications, lobular borders, tall morphology, hypoechogenicity, and solid composition. Their combination is required for an informed decision regarding biopsy as one alone is not sufficient; hence, the need for guidelines for the various combinations for better identification of a malignant nodule [5].

During the past 11 years, several ultrasound-based risk-stratification systems have been developed to provide clinicians with recommendations regarding the need for a biopsy [6-8]. Previous studies that compared the accuracy of various systems for thyroid nodules reported mixed results [5,9-11]. Two popular systems used in our department are the American Thyroid Association system (ATA2015), and the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS).

The ATA2015 guidelines are based on sonographic patterns: echogenicity, echostructure, the presence/absence of microcalcifications, margins, and shape. Nodules are classified according to these patterns into 5 categories: benign (cyst), very low suspicion (< 3% malignancy), low suspicion (5–10% malignancy), intermediate suspicion (10–20% malignancy), and high suspicion (70–90% malignancy).When coupled with nodule size, these categories inform clinicians about which nodules can be managed by observation and which need to be biopsied by FNA [2].

In ACR TI-RADS, sonographic features (nodule composition, echogenicity, shape, margin, presence of echogenic foci) are assigned points according to the suspicion of malignancy. The total number of points is summed to determine the nodule's risk level. Risk levels range from TR1 (benign) to TR5 (high suspicion of malignancy). Recommendations for biopsy or follow-up are decided according to the risk level and the nodule size [10,12].

We compared the diagnostic performance of the ATA2015 with that of the ACR TI-RADS in a large series of patients who underwent thyroidectomy in a single center.

PATIENTS AND METHODS

The database of Emek Medical Center was scanned for the medical records of patients who had undergone partial (lobectomy) or subtotal or total thyroidectomy between January 2012 and March 2019. Notably, 2012 was the first year that physicians in the department began practicing FNA guided by ultrasound of thyroid nodules. The decision to perform surgery was based on the cytology of the thyroid nodule, the patient's complaints, physical examination, and risk factors. One inclusion criterion was the availability of sufficient data, which could be either a preoperative, detailed ultrasound report, containing all the sonographic features included in the aforementioned risk-stratification system or recorded preoperative pictures of the nodules on the ultrasound hard disc with sufficient details to determine the exact classification in each of the risk-stratification systems. Other inclusion criteria were postoperative surgical pathology of a differentiated thyroid carcinoma and the presence of 1–3 nodules in the excised lobe. Excluded were thyroidectomies performed due to non-thyroid disease and non-differentiated thyroid lesions (lymphoma, anaplastic, amyloidosis).

Thyroid ultrasound examination ultrasound examinations were performed using GE LOGIC 8 (GE Healthcare, Milwaukee, WI, USA), equipped with a 5–12 MHz linear array transducer. Detailed sonographic data were recorded only for the nodules that had been FNA-biopsied (nodules that were not aspirated were not fully described).The following sonographic data were recorded for each nodule: echogenicity, composition, type of margins, calcifications, shape (taller than wider), and the largest diameter. Sonographic data of examinations performed from January 2012 to March 2016 were abstracted from written reports filed by the otorhinolaryngologists who performed the examinations. From April 2017 to March 2019, representative pictures of the nodules were saved on the hard disk of the ultrasound machine, making available pictures that enabled evaluation of the sonographic data of each nodule. Only good quality ultrasound images were included.

Ultrasound examinations were performed by one of three otorhinolaryngologists (DA,LS,MP) who had extensive experience (more than 500 examinations altogether) with ultrasound FNA of the thyroid. Sonographic data, either from written reports or ultrasound images, were independently reviewed by two otorhinolaryngologists (MP, RG) who routinely interpret thyroid ultrasound images. In the event of disagreement about a particular ultrasound feature, a third party was consulted (LS).

Ultrasound features of nodules were reviewed and classified according to the ATA2015 and the ACR TI-RADS 2017 systems, while blind to the FNA and postoperative pathology results. The need to biopsy a certain nodule was determined according to the guidelines for each scale individually. After referring to the five relevant sonographic characteristics of each stratification system, we entered (if needed) the largest diameter of the nodule into the equation and then determined whether the scale's recommendation was to perform a biopsy or not. In order to compare the scoring systems, TR1 of the ACR TI-RADS 2017 system was considered analogous to the ATA2015 *benign* category, TR2 to the very low suspicion category; TR3 to *low suspicion*; TR4 to *intermediate suspicion*; and TR5 to *high suspicion.*

STATISTICAL ANALYSIS

Quantitative data are presented as means ± standard deviations. Qualitative data are presented as frequencies. Patient's age and nodular size were compared between two groups using chi-square test for categorical variables and *t*-test for two independent samples for continuous variables. Percentage difference between the calculated and the expected malignancy rate was calculated by chi-square test. When the percentage was significant, standardized residual analysis was applied to find the source of the difference. Sensitivity of scale was defined as the ability to correctly recommend biopsy for a malignant nodule (true positive/all malignant cases). Specificity of a scale was defined as the ability to correctly recommend against biopsy for a benign nodule (true negative/all benign cases). Positive predictive value (PPV) was applied to cases in which a scale correctly recommended biopsy for a malignant nodule out of total times it recommended biopsy (for malignant + benign nodules)–(true positive/all cases of biopsy). Negative predictive value (NPV) was indicated for cases in which a scale correctly recommended against biopsy for a benign nodule out of total times it recommended against biopsy (for benign and malignant nodules) (true negative/all cases of benign nodules). Diagnosis of certain nodule began with a division into five levels according to the sonographic features. The five categories of each scale (e.g., high suspicion, intermediate suspicion, low suspicion) were followed. Next, and after considering the size, we determined whether a biopsy would be needed (necessary or not necessary). Therefore we switched from a 5-level scale to a 2-level binary decision.

Sensitivity, specificity, PPV, and NPV were calculated by comparing pathology findings. The receiver operating characteristic (ROC) curve was used to compare diagnostic values of the guidelines, according to the value of Kappa. The odds ratio (OR) was calculated to compare the sonographic recommendation with the standard reference diagnosis (malignant vs. benign). Statistical significance was assumed when $P < 0.05$. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

DEMOGRAPHIC FEATURES

Of 305 patients (338 nodules) who underwent lobectomy or subtotal or total thyroidectomy, 89 patients were excluded from the analysis for the following reasons: no preoperative ultrasound was performed at our center (n=42); no nodules were observed (Grave's disease, enlarged thyroid lobe, completion thyroidectomy) (n=19); there were more than four nodules (Hashimoto thyroiditis, multinodular goiter) (n=18); thyroidectomy was performed due to non-thyroid disease (such as parathyroidectomy) (n=7); non-differentiated thyroid lesions presented (lymphoma, anaplastic, amyloidosis) (n=3).

The final cohort consisted of 216 patients (238 nodules), including 171 females (80%) [Figure 1]. Mean ages of the benign group and the malignant group were 50.0 ± 12.4 years and 50.7 ± 16.7 years, respectively (P = 0.7). Of the 238 nodules, 115 (48.3%) were malignant: 58 of the normal papillary variant, 17 of the follicular variant of papillary carcinoma, 14 of the tall cell variant of papillary carcinoma, 6 follicular carcinomas (4 minimally invasive and 2 widely invasive), and 2 medullary carcinomas. Eighteen nodules were metastatic carcinomas. The mean size of the benign nodules was larger than that of the malignant nodules: 33.0 mm vs. 23.1 mm (P < 0.001).

MALIGNANCY RISK STRATIFICATION

Table 1 summarizes the number of nodules classified into each category of the sonographic systems, the calculated rates of malignancy (ROM), and the expected malignancy risk according to previous reports [13-15]. The calculated malignancy rates were higher than the expected malignancy risks for two ACR TI-RADS categories: 59.6% vs.5.1–20.0% for TR4 (P < 0.001), and 7.5% vs. P < 2.0% for TR2. For the ATA2015 system, the observed malignancy risk for the intermediate suspicion category was significantly higher than the expected malignancy risk: 55.5% vs. 10.0–20.0% (P < 0.001).

COMPARISON OF THE NEED FOR BIOPSY FOR BENIGN AND MALIGNANT NODULES ACCORDING TO THE ATA2015 AND ACR TI-RADS SYSTEMS

According to the ATA2015 scale, 88.7% (197/222) of all the nodules needed to be biopsied. The percentages of the malignant nodules and the benign nodules that needed to be biopsied were 93.3% and 84.4%, respectively. Sixteen nodules could not be categorized, 9 of them malignant. According to the ACR TI-RADS scale, 64.7% (154/238) of the nodules needed to be biopsied, 84.3% of the malignant, and 46.3% of the benign nodules [Figure 2].

DIAGNOSTIC PERFORMANCE

True positive was defined when a nodule recommended by the scale for biopsy turned out (after surgery and final histology examination) to be malignant. True negative was defined when a nodule not recommended by the scale for biopsy turned out to be benign. False positive was defined when a nodule recommended by the scale for biopsy turned out to be benign, and false negative was defined when the scale did not recommend biopsy and it turned out to be malignant.

Figure 1. Flow diagram of study participants

ACR TI-RADS = American College of Radiology Thyroid Imaging Reporting and Data System
ATA = American Thyroid Association

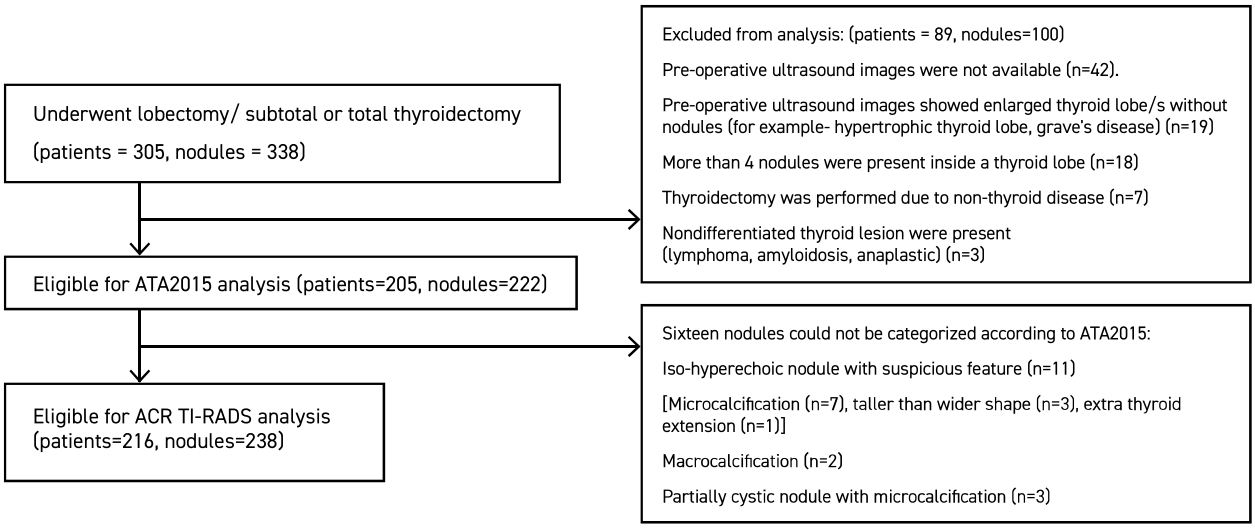

Table 1. Malignancy risk according to the ACR TI-RADS and ATA2015 classification systems [15]

	Number of nodules	Malignant nodules	Statistical tests	Calculated malignancy rate (%)	Expected malignancy rate (%)*	*P* value***
ACR TI-RADS	238	115	chi-square = 63.14*			
5	81	73	1.72**	90.0	< 20	0.1711
4	57	34	-7.02**	59.6	5.1–20	0.0001
3	35	4	-2.38**	11.4	5	0.0446
2	53	4	-2.2**	7.5	< 2	0.0001
1	12	0	0.22**		0	0.4129
ATA2015	222	106	chi-square = 118.17*			
High suspicion	76	70	-0.96**	92.1	> 70–90	0.0427
Intermediate suspicion	45	25	-10**	55.5	10–20	0.0001
Low suspicion	47	8	-1.7**	17	5–10	0.0174
Very low suspicion	44	3	-3.5**	6.8	< 3	0.0244
Cyst	10	0	0.24**	0	< 1	0.5871
Not included	16	9		56.2%		

*Significant value
**Standardized residual analysis. Value > 2.57 (absolute) means significant difference
****P* ≤ 0.05 was considered statistically significant
ACR TI-RADS = American College of Radiology Thyroid Imaging Reporting and Data System
ATA = American Thyroid Association

Figure 2. The need for biopsy of benign and malignant nodules, according to the ACR TI-RADS and ATA classification systems

ACR TI-RADS = American College of Radiology Thyroid Imaging Reporting and Data System

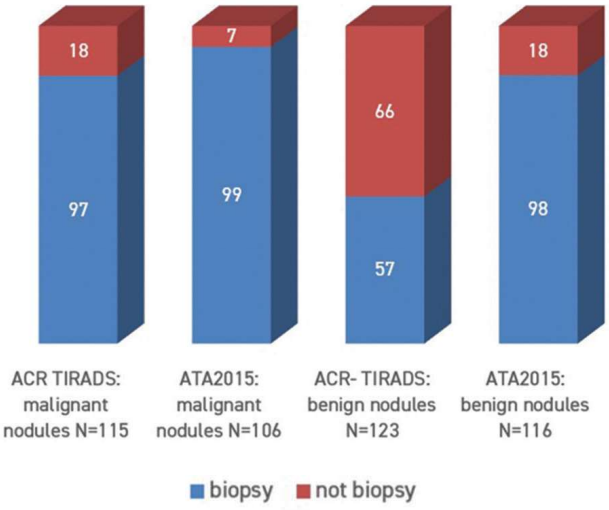

Table 2 summarizes the diagnostic performance of the two risk stratification systems. The ACR TI-RADS sonographic pattern demonstrated higher specificity, PPV, and NPV. The ATA2015 sonographic pattern yielded higher sensitivity. According to the ROC curve analysis, the areas under the curve (AUC) of the ACR TI-RADS and ATA2015 categories were 0.89 ± 0.021 and 0.90 ± 0.021, respectively. This difference in AUC was not statistically significant. Of the 18 cases of malignancy missed by ACR TI-RADS (false negative rate 15.6%), 4 had aggressive behavior (either metastatic cancer or tall cell variant): 3 classified as TR5, and 1 classified as TR4. Of the 7 malignancies missed by ATA2015 (false negative rate 6.6%), 3 had aggressive behavior: 1 classified as high suspicion, 1 classified as intermediate suspicion, and 1 case classified as low suspicion.

DISCUSSION

The vast majority of thyroid carcinoma cases are non-aggressive, making it the cardinal role of a risk stratification system to identify aggressive cancers. A main finding of the present study was that the two classification systems examined identified aggressive cancers at the same rate. Applying the ACR

Table 2. Diagnostic efficacy of the ATA2015 and ACR TI-RADS systems

	ATA2015	ACR TI-RADS
Nodules biopsied, N	222	238
True positive cases (%)	99/106	97/115
True negative cases (%)	18/116	66/123
False positive cases (%)	98/116	57/123
False negative cases (%)	7/106	18/115
Sensitivity	0.933	0.843
Specificity	0.155	0.536
Positive predictive value	0.502	0.629
Negative predictive value	0.72	0.785
Odds ratio	2.59	6.23
Confidence interval	1.03–6.49, $P < 0.05$	3.37–11.54, $P < 0.001$

ACR TI-RADS = American College of Radiology Thyroid Imaging Reporting and Data System
ATA = American Thyroid Association

TI-RADS scale yielded ROM in three categories: 1 (benign), 3 (low suspicion), and 5 (high suspicion), in line with the expected malignancy rates [15]. However, higher than expected ROM was demonstrated in categories 2 (very low suspicion) and 4 (intermediate suspicion).

In contrast, the ATA2015 scale showed higher than expected ROM in category 4 (intermediate suspicion). This finding, which is in agreement with data reported by other researchers [9,11], has a number of possible explanations:

- The underestimation of ROM in solid hypoechoic nodules, which were present in the intermediate suspicion and TR4 categories. Higher ROMs in these categories were also reported in other studies [13,14].
- The higher ROM of the TR2 group on the ACR TI-RADS scale may be due to the lack of differentiation between partially cystic nodules. While cystic nodules both with and without eccentric solid areas are classified as TR2, earlier studies clearly demonstrated more malignancy for partially cystic thyroid nodules that contain an eccentric solid portion compared to those without this sign. Malignancy rates associated with eccentric solid areas have been reported in the range of 7–23% [15,16].
- The inclusion in the cohort of patients who had been referred to our tertiary medical center for operations raises the possibility of bias. The higher rate of confounding factors, such as family history of thyroid cancer and related symptoms, which are more common in our patients than in a population treated in hospitals that are not tertiary medical centers, could impact malignancy rates.

An important finding of our study is that the biopsy threshold was higher in the ACR TI-RADS system than in the ATA2015 system, in concurrence with previous publications [17,18]. When the two systems were compared, the ACE TI-RAD would have had to perform 38.1% more biopsies for benign lesions and 24%more biopsies for all nodules to reach the threshold of the ATA2015 system. Our results concur with those of a Korean study [19], which compared seven stratification systems, including ACR TI-RADS and ATA2015, in an evaluation of 2000 nodules. Their study showed 26.4% fewer unnecessary biopsies using ACR TI-RADS compared to ATA2015 [19]. This finding is congruent with an important premise of the ACR TI-RADS philosophy, namely, missing thyroid cancers may be acceptable since most of them are indolent or nonaggressive.

As expected, the false negative rate in our series was higher with ACR TI-RADS than ATA2015: 15.6% vs. 6.6%. However, considering the nine cancers that were missed by the ATA2015 system due to the inability to classify the nodules, the false negative rate of ATA2015 rises to 13.9%. Interestingly, false negative rates of only the high-risk carcinomas (lymph node metastasis, aggressive variants) were identical for the two systems, 3.4%. Four cases of aggressive carcinoma were missed by each system (1 case of metastatic carcinoma could not be classified using the ATA2015 system).

The diagnostic performance of the ATA2015 scale showed high sensitivity and very poor specificity rates (93% vs. 15%), reflecting its low biopsy thresholds. The ACR TI-RADS scale, however, showed lower sensitivity and a much higher specificity rate (84% vs. 53%). These results reflect ACR TI-RAD's better performance as a rule-out tool; that is, a scale that can better identify benign nodules and thereby reduce the need for biopsy. This finding broadly supports the work of other studies that showed a much higher specificity rate and lower sensitivity rate of the ACR TI-RAD scale compared to the ATA2015. Combining the results of these studies, the reported ranges of sensitivity of ACR TI-RADS and ATA2015 are 74.0–81.6% and 89.6–95.5%, respectively. The reported ranges of specificity are 47.0–79.7% and 10.0–73.0%, respectively [8-10]. The AUCs and ORs of both systems reflect their ability to discriminate between benign and malignant nodules.

A significant drawback of the ATA2015 scale is its inability to classify every nodule. Previous studies documented a 3–14% rate of unclassifiable nodules [4,12]; importantly, the ROM of ATA 2015- unclassified nodules ranged from 9.4% to 46.7%, respectively [8,19]. In the present study, 6.7% of all nodules could not be classified using the ATA2015 scale; 56.2% (9 of 16) of them were malignant, one of which was a high-risk carcinoma (metastatic carcinoma). The most common sonographic pattern of those non-classified nodules included a combination of iso + hyperechogenicity with microcalcifications (5 of 9). The high ROM of this group may have been biased by the high ROM of our cohort due to the hospital being a tertiary medical center drawing cases referred for surgery.

LIMITATIONS

There are a number of limitations to our study. For one, it is a single institution, retrospective study with a relatively small cohort. In addition, the fact that it is a tertiary referral center may have led to the higher ROM and therefore a higher than expected PPV. Third, nodules were interpreted according to static images and not by recorded video clips. Additional images of the latter type may have changed our interpretations of the data.

CONCLUSIONS

We documented higher ROM than expected from the literature in ACR TI-RADS categories 2 and 4, and in ATA2015 intermediate suspicion category, and more biopsies with the ATA scale (38.1% more for benign nodules and 24.3% more for all nodules) than with the ACR TI-RADS scale. It follows that the ACR TI-RADS scale had more false negative cases (18 cases vs.7 cases), although the percentage of aggressive cancer cases that were missed by the two systems were almost the same (4 by ACR TI-RADS vs. 3 by ATA2015), These data are intended to help clinicians select the optimal risk stratification system, taking into consideration the clinical characteristics of the patients.

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Capsule

Gut inflammation locking down access to the brain

Inflammatory bowel disease is best known for intestinal symptoms but can also cause a variety of extra-intestinal manifestations in other organs. It can also be associated with cognitive and psychiatric effects, including anxiety and depression. Using mouse models of intestinal inflammation, **Carloni** co-authors uncovered a potential pathogenic link between these aspects of inflammatory bowel disease. The inflammatory process causes the gut vascular barrier to become more permeable, resulting in the spread of inflammation beyond the intestine, while the vascular barrier in the choroid plexus shuts down, helping to protect the brain from inflammation but also potentially impairing communication between organs and impairing some brain functions.

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