American Journal of Otolaryngology and Head and Neck Surgery

Research Article
Published: 18 Oct, 2021

Ultrasound Assessment of Thyroid Nodules and Cytological Correlation: Comparative Study between ACR and EU-TIRADS 2017

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Abstract

Purpose: To evaluate the diagnostic accuracy of ACR (American College of Radiology) and EU (European)-TIRADS 2017 by correlating the ultrasound data to the cytological findings and to study the agreement of these two systems for predicting malignancy.

Materials and Methods: A prospective and analytic study was conducted at the radiology department of Charles Nicolle University hospital from November 2020 to June 2021.

All the nodules included in the study had been classified according to the ACR-TIRADS guidelines before Fine Needle Non Aspiration Cytology (FNNAC). Then, ultrasound findings were reclassified according to the EU-TIRADS. The cytological results were categorized according to BETHEZDA 2018.

The Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of TIRADS systems and their statistical relationship with the cytological results were calculated. The study of the agreement between the two systems was performed by Cohen's Kappa coefficient.

Results: Our study included 124 nodules (120 patients, 87.5% women with average age of 53.1 years). The distribution of the nodules according to the ACR-TIRADS was respectively 22%, 55% and 23% for TIRADS (TR) 3, TR4 and TR5. According to EU-TIRADS, it was respectively 26%, 36% and 38%. The cytological results were respectively 31.5%, 35.5%, 6.5%, 12.9%, 9.7% and 4% for the Bethesda 1, 2, 3, 4, 5 and 6 categories. Excluding Bethesda 1, 3 and 4 nodules, a statistically significant relationship between the ultrasound risk level of both TIRADS and the cytological result was established. By proceeding in the same way, the sensibility, specificity, PPV and NPV were almost similar for both TIRADS systems and respectively: 100%, 36.4%, 37.8%, 100% for ACR-TIRADS and 100%, 31.8%, 36.1% and 100% for EU-TIRADS. The agreement between the two systems was good and no significant difference was noticed.

Conclusion: This study confirmed the excellent sensitivity of both TIRADS with a NPV approaching 100% to avoid unnecessary FNNACs. The agreement between ACR and EU-TIRADS 2017 was good with equivalent diagnostic value.

Introduction

A thyroid nodule is a localized hypertrophy of the gland. It is a common pathology in clinical practice with a clear preponderance of women.

The prevalence of the thyroid nodule depends on the diagnostic method: it can be palpated only in 4% of adults, 50% of autopsy studies and 67% in ultrasound using a high frequency ultrasound probe [1,2].

Among these nodules, the risk of malignancy is close to 5% [3]. Therefore, it would be unacceptable to explore surgically all the nodules, given the high cost of the procedure and the risks inherent to surgery.

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Received Date: *15 Sep 2021*
Accepted Date: *05 Oct 2021*
Published Date: *18 Oct 2021*

Citation:
Azzouz E, Jrad M, Zlitni H, Boukriba S, Frikha W, Boumediene M, et al. Ultrasound Assessment of Thyroid Nodules and Cytological Correlation: Comparative Study between ACR and EU-TIRADS 2017. Am J Otolaryngol Head Neck Surg. 2021; 4(9): 1160.

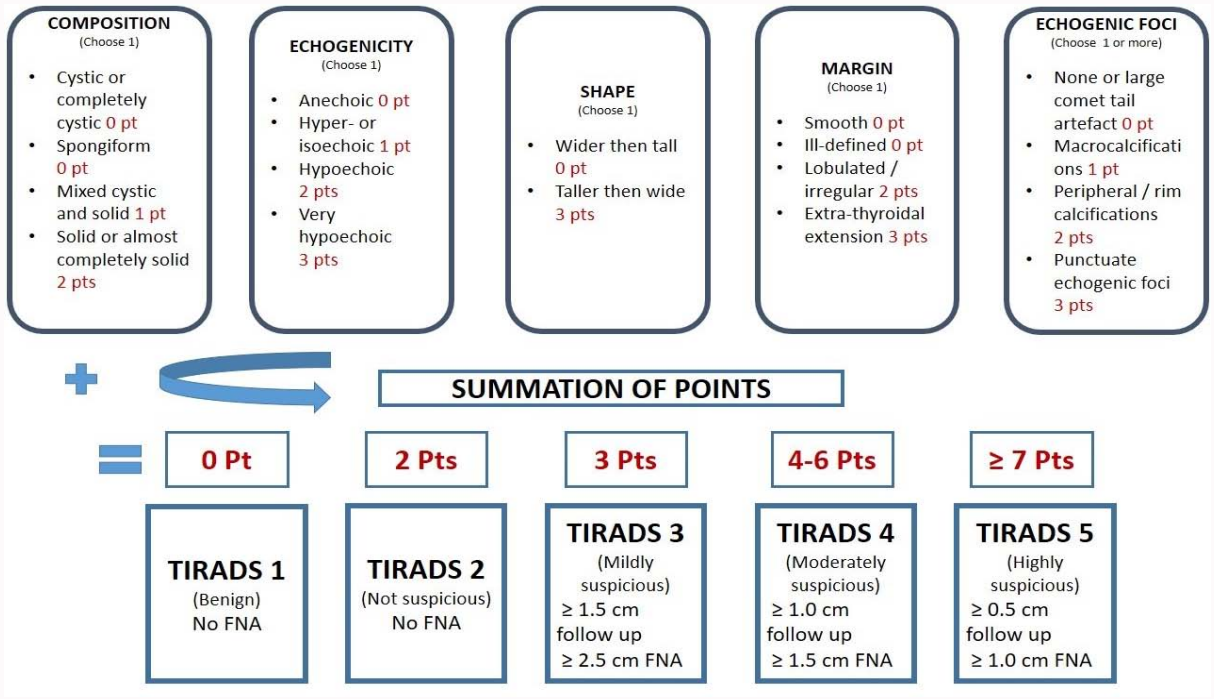

Figure 1: ACR TI-RADS scoring system diagram.

The Thyroid Imaging Reporting and Data systems (TIRADS), of which an update was published in 2017 by the American College of Radiology (ACR-TIRADS) and the European Thyroid Association (EU-TIRADS) represent a selection method of nodules that justify a cytological diagnosis based on ultrasound criteria suggestive of malignancy.

Thyroid Fine Needle Non Aspiration Cytology (FNNAC) is an effective way to estimate the likelihood of benignity or malignancy based on the Bethesda 2018 cytological classification. It is a simple, fast, reliable and minimally invasive technique.

The purpose of this study was:

- To evaluate the diagnostic accuracy of the ACR-TIRADS and EU-TIRADS 2017 classifications by reference to the cytological results of thyroid nodules.
- To study the agreement between these two systems for the malignancy risk stratification of thyroid nodules.

Materials and Methods

It was a prospective and analytic study conducted at the radiology department of Charles Nicolle University Hospital from November 2020 to June 2021.

Patients

124 thyroid nodules in 120 patients were included.

We prospectively collected nodules in patients over the age of 18 who had cervical ultrasound and thyroid FNNAC including [4]:

- Patients followed at the Ear, Nose and Throat (ENT), Endocrinology and Internal Medicine Departments and referred to the Radiology Department for an aspiration of a known thyroid nodule.
- Patients referred for cervical ultrasound and in whom a thyroid nodule validating the ACR-TIRADS criteria for thyroid FNNAC has been discovered (Figure 1).

For statistical operations requiring a binary cytological result (benign or malignant nodule), non-diagnostic or unsatisfactory samples (Category 1 of Bethesda) and nodules of indeterminate cytology (Bethesda 3 and 4 categories) have been excluded from the starting population. We established:

- The relation between the age of the patient, the gender and the size of the nodule on the one hand and the cytological result on the other hand.
- The diagnostic accuracy of the TIRADS systems.
- The relation between the TIRADS score and the cytological result.

However, the agreement study between ACR-TIRADS and EU-TIRADS 2017 has interested all the nodules of the starting population without taking into account the cytological result.

US-examination and US-guided FNNAC procedures

Us-examinations were performed with a 7 MHz to 12 MHz linear array transducer (TOSHIBA XARIO 200) by senior physicians and radiology residents. The following features were assessed: composition, echogenicity, shape, margins and echogenic foci of thyroid nodules in order to give them ACR-TIRADS score [5,6]. Then, the size in two orthogonal (axial and sagittal) planes was noted. Finally, the lateral cervical region was explored for lymphadenopathy.

Thyroid FNNAC was performed immediately following cervical ultrasound. All patients were informed of the course and potential complications of the procedure (moderate pain, risk of peri-thyroid hematoma…). No special preparation was necessary and antiaggregant and/or anticoagulant treatment was maintained. However, if the INR had to be greater than 2, the relay by a curative

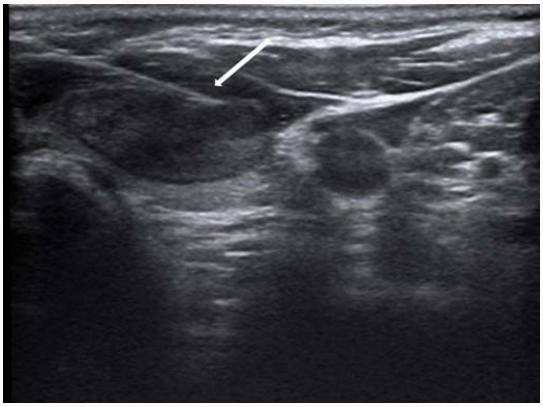

Figure 2: Ultrasound control of the needle path. The very hypoechoic portion was targeted (arrow).

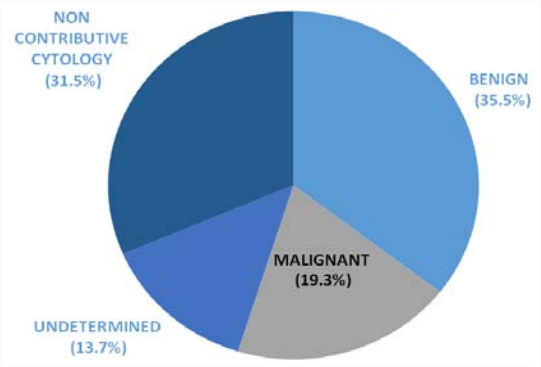

Figure 3: Distribution of nodules according to the benign or malignant nature of cytology.

dose of Low Molecular Weight Heparin (LMWH) after skipping a dose before the gesture was recommended [7].

According to the guidelines of the ACR [5], the indication of a FNNAC was based on the TIRADS level and the maximum diameter of the nodule:

- TIRADS 3 if the largest diameter was greater than 25 mm,
- TIRADS 4 if the largest diameter was greater than 15 mm,
- TIRADS 5 if the largest diameter was greater than 10 mm.

We introduced a 25-gauge needle longitudinally, in line with the long axis of the transducer (Figure 2). Solid portion of mixed nodules and parts with the most pejorative aspect were targeted. We avoided active aspiration and relied on capillary tension to suck the tissue sample into the needle bore [8]. FNNAC was performed at least twice for each nodule to optimize the quality of the sample. The slides thus obtained were sent to the anatomical pathology department.

The smears were analyzed after MGG (May-Grünwald Giemsa) and PAP (Papanicolaou) stains. The cytological results were presented as 6 groups defined by the Bethesda classification published in 2018 [9,10].

Retrospectively, we were able to determine the EU-TIRADS level of studied nodules from the detailed reports of thyroid echography and JPEG ultrasound images [11].

Data and statistical analysis

The statistical analysis of data was done by using SPSS program (Statistical Package for Social Science version 22.0).

Epidemiological data were presented as the mean ± standard deviation.

Cytopathology results from US-guided FNNAC were considered the standard of reference. For the statistical analysis, the Bethesda 5 and 6 categories were combined as malignant group, Bethesda 2 category was considered the benign group and Bethesda 1, 3 and 4 categories were excluded.

The relation between the age, the gender of the patient and the size of the nodule on the one hand and the cytological result on the other hand was evaluated through double entry tables, χ^2 and Pearson's correlation tests.

We also determined the diagnostic accuracy of the ACR-TIRADS and EU-TIRADS 2017 systems based on true positive, true negative, false positive and false negative results.

The relation between the TIRADS categories and the cytological results was then assessed. The non-parametric Mann-Whitney test was used to examine whether the risk of malignancy increased with the ACR-TIRADS score.

We transformed the quantitative variable ACR-TIRADS score into qualitative variable with two modalities to establish the Receiver Operating Characteristics (ROC) curve. We chose as a threshold the value of the variable that corresponds to the best "sensitivity-specificity" pair. Finally, we studied the agreement between ACR-TIRADS and EU-TIRADS 2017 for the malignancy risk stratification of thyroid nodules by using Cohen k coefficient.

All tests were two-sided, and a significance level of p=0.05 was used.

Results

Since this study relied only on cytological results, we considered Bethesda 1 as non- contributive cytology, Bethesda 2 nodules as benign, Bethesda 3 and 4 nodules as undetermined and nodules classified Bethesda 5 and 6 as malignant. This distribution is summarized in Figure 3.

The clinical characteristics of the 120 patients (124 nodules) were as follow: the mean age was 53.1 ± 13.6 years (range 18 to 80) and 87.5% were female. The mean size of nodules was 23.5 mm ± 10.6 mm (range 10 to 58).

The prevalence of thyroid nodules was much lower in men than in women, but nodules found in male patients had a significantly higher rate of malignancy (63% malignant nodules *vs.* 23% in women, P=0.03).

There was no statistically significant relationship between the age of patients and malignancy (P=0.29). Likewise, malignant nodules were not significantly larger than benign ones (P=0.15).

Nodules were classified as ACR-TIRADS 3, 4 and 5 in 22, 55, and 23% of cases respectively (Figures 4-6). Posteriorly, nodules were re-classified as EU-TIRADS 3, 4 and 5 in 26, 36 and 38 % cases respectively.

The cytological descriptive statistics results were as follow: 31.5% (n=39) non-diagnostic (Bethesda 1), 35.5% (n=44) benign (Bethesda 2), 6.5% (n=8) atypia of undetermined significance (Bethesda 3),

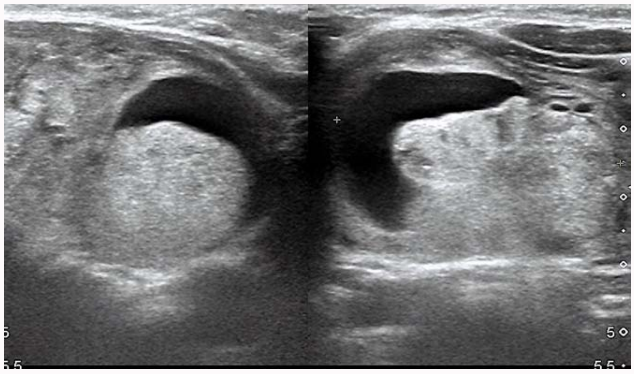

Figure 4: ACR-TIRADS 3: Mixed nodule with solid isoechoic portion.

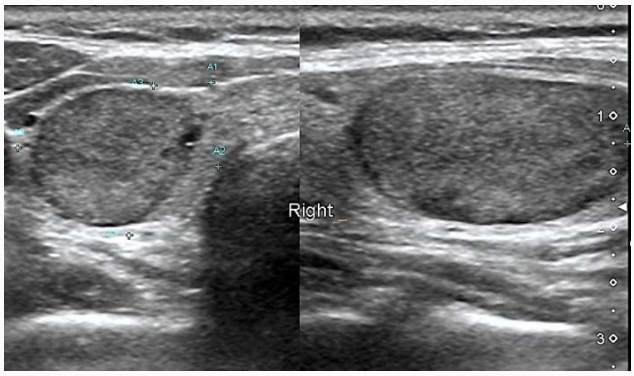

Figure 5: ACR-TIRADS 4: Solid hypoechoic nodule with smooth margins.

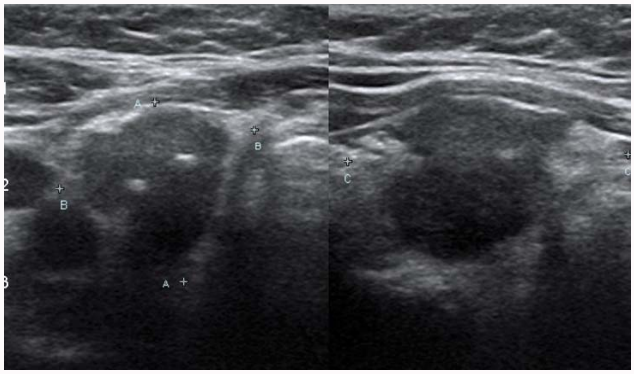

Figure 6: ACR-TIRADS 5: Solid and very hypoechoic nodule with irregular margin.

12.9% (n=16) suspicious for a follicular neoplasm (Bethesda 4), 9.7% (n=12) suspicious for malignancy (Bethesda 5) and 4% (n=5) malignant (Bethesda 6) (Figures 7-11).

All nodules suspicious for malignancy and malignant Bethesda 5 and 6 were classified TIRADS 4 and 5 for both ACR and EU systems (Table 1, 2).

Considering TIRADS 3 as probably benign US finding, and TIRADS 4 and 5 as probably malignant US findings as shown in Table 3, 4, the sensitivity, specificity, positive predictive value and negative predictive value were calculated. For ACR-TIRADS, they were respectively 100%, 36.4%, 37.8% and 100%. For EU-TIRADS, the same parameters were respectively: 100%, 31.8%, 36.1% and 100% (Table 5).

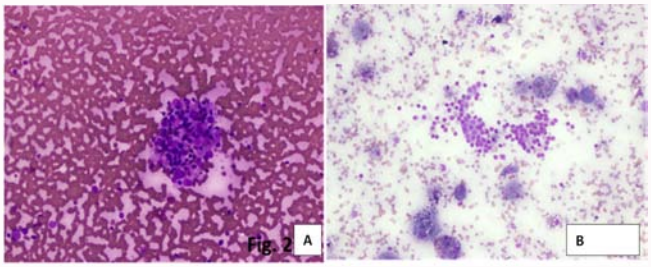

Figure 7: Bethesda 2; A. Lymphocytic thyroiditis; B. Benign follicular nodule.

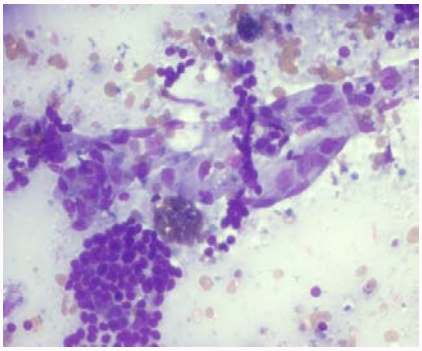

Figure 8: Bethesda 3 Atypia of Undetermined Significance (AUS).

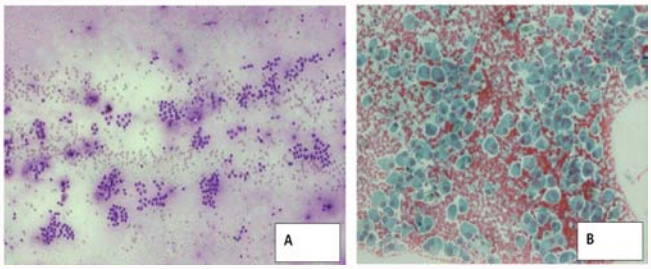

Figure 9: Bethesda 4; A. Follicular neoplasm; B. Follicular neoplasm Hürthle Cell (Oncocytic) Type.

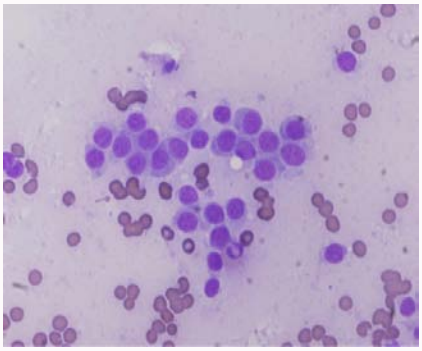

Figure 10: Bethesda 5 suspicious for medullary thyroid carcinoma.

By proceeding in the same way, a statistically significant relationship between the ultrasound risk level of both TIRADS and the cytological result was established (P=0.003).

ACR-TIRADS point total was significantly higher in the malignant group (mean, 7.12 ± 2.49; range, 4 to 14 points) in comparison with the benign group (mean, 5 ± 2.2 points; range 2 to 10 points) (P=0.003).

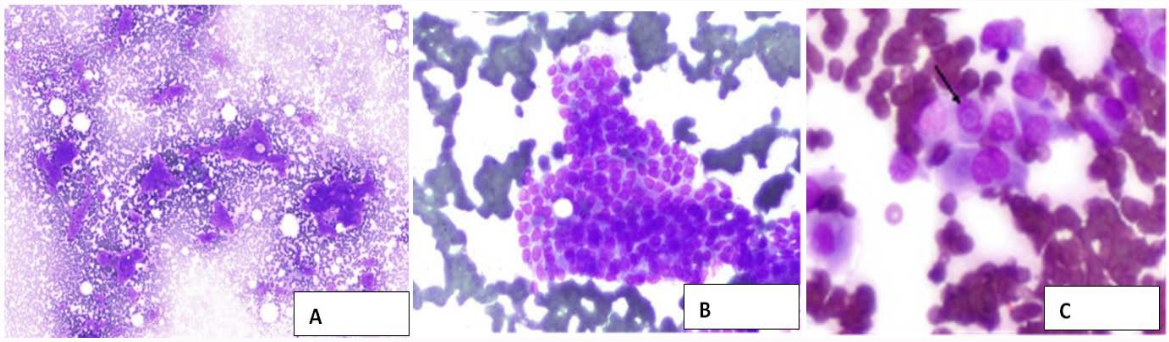

Figure 11: Bethesda 6 papillary thyroid carcinoma.

Table 1: Joint distribution of ACR-TIRADS and Bethesda categories.

	BETH 1	BETH 2	BETH 3	BETH 4	BETH 5	BETH 6	Total
ACR-TR3	5	16	1	5	0	0	27
ACR-TR4	32	15	6	8	6	1	68
ACR-TR5	2	13	1	3	6	4	29
Total	39	44	8	16	12	5	124

Table 2: Joint distribution of EU-TIRADS and Bethesda categories.

	BETH 1	BETH 2	BETH 3	BETH 4	BETH 5	BETH 6	Total
EU-TR3	9	14	5	4	0	0	32
EU-TR4	24	10	1	8	2	0	45
EU-TR5	6	20	2	4	10	5	47
Total	39	44	8	16	12	5	124

The ROC curve thus established is shown in Figure 12. The area under the curve =0.74 was significantly greater than 0.500 (P=0.004 and 95% confidence interval between 61% and 86%). We determined a cut-off threshold value of 5 points from which the risk of malignancy increased significantly with a sensitivity of 88% and a specificity of 53%.

Both systems reported the same TIRADS level for 91 of the 124 nodules that were studied which represented 73% of the total (Table 6). Concordance between the ACR-TIRADS and EU-TIRADS ultrasound risk stratification systems was measured using Cohen's Kappa coefficient (K). The un-weighted Kappa was 0.59 expressing moderate agreement between the two systems. The Kappa with linear and quadratic weighing was 0.66 and 0.75 respectively, expressing good agreement between the two systems.

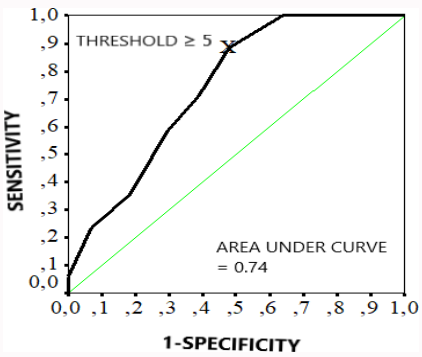

Figure 12: Receiver Operating Characteristic (ROC) curve of the number of ACR-TIRADS points according to the cytological result.

Table 3: ACR-TIRADS categories and risk of malignancy.

	Benign	Malignant	Total
ACR-TIRADS 3	16	0	16
ACR-TIRADS 4+5	28	17	45
Total	44	17	61

Table 4: EU-TIRADS categories and risk of malignancy.

	Benign	Malignant	Total
EU-TIRADS 3	14	0	14
EU-TIRADS 4+5	30	17	47
Total	44	17	61

Table 5: Diagnostic accuracy of ACR and EU-TIRADS.

Parameter	ACR-TIRADS	EU-TIRADS
Sensitivity (%)	100 [81 to 100]	100 [81 to 100]
Specificity (%)	36.4 [23 to 51]	31.8 [20 to 46]
PPV (%)	37.8	36.1
NPV (%)	100	100

Discussion

Studies have shown that the diagnostic accuracy of the Bethesda system is discriminatory between benign and malignant nodules [12,13]. The Bethesda system offers good sensitivity (77%) and excellent specificity (98.7%) and NPV (97.8%) with a low false negative rate (2.2%) [14].

The distribution of the different Bethesda categories in our series

Table 6: Cross-tabulation between ACR-TIRADS and EU-TIRADS categories.

	ACR-TR 5	ACR-TR 4	ACR-TR 3	Total
EU-TR 5	29	18	0	47
EU-TR 4	0	40	5	45
EU-TR 3	0	10	22	32
Total	29	68	27	124

and according to the Bethesda guidelines is summarized in Table 7.

We had a high rate of inadequate sampling (Bethesda 1) despite the two passages imposed for FNNAC. This could be explained by inter-operator variability and manipulator experience [16]. However, the low proportion of benign nodules in our series compared to literature data suggests a high rate of benign nodules among non-diagnostic specimens. For the proportions of nodules of indeterminate cytology (Bethesda 3 and 4) and those of cytology suspected of malignancy (Bethesda 5) and malignant (Bethesda 6), our results are consistent with those in the literature.

According to the Bethesda 2018 review [9,10], the risk of malignancy of the different categories is as follows: 5% to 10% in the Bethesda 1 category, 0% to 3% in the Bethesda 2 category, 10% to 30% in the Bethesda 3 category, 25% to 40% in the Bethesda 4 category, 50% to 75% in the Bethesda 5 category and 97% to 99% in the Bethesda 6 category.

Considering the TIRADS 3 level as low ultrasound risk and by grouping the TIRADS 4 and 5 levels together (high ultrasound risk), we were able to demonstrate a statistically significant relationship between the ultrasound risk and the malignant or benign cytological result of the nodules for both TIRADS systems (p=0.003). The risk of malignancy is greater in the high-risk ultrasound category. Therefore, if a nodule is correctly classified according to TIRADS, the probability of malignancy deduced will be accurate.

Our results confirm that both TIRADS systems are highly sensitive with excellent NPV. Therefore, TIRADS systems are ultrasound screening tests for nodules suspected of malignancy and candidates for a thyroid FNNAC: They miss very few malignant nodules. However, they have a low specificity leading to a high rate of false positives that will be "cleared" by highly specific cytology. Moreover, the excellent NPV offers a security for the benign nature of the nodule if the echographic aspect is reassuring (in this case TIRADS 3).

We concluded that the risk of malignancy increased with the sum of ACR-TIRADS score points. From the established ROC curve, we determined a cut-off value of 5 points from which the risk of malignancy increased significantly with a sensitivity of 88% and a specificity of 53%. This new threshold shows a timid gain in specificity compared to the classification into 5 categories of the ACR-TIRADS in our study (36.4%). However, it shows a clear decrease in sensitivity that was previously close to 100%. The increase in the sum of ACR-TIRADS points reflects the increased risk of malignancy of the nodule if coexistence of several suspect ultrasound criteria. This has been demonstrated in a few publications before the advent of the ACR-TIRADS [17,18].

In our study, the two systems indicated the same TIRADS category for 87 of 124 nodules studied, i.e. 70% of the total. The un-weighted kappa was 0.55 expressing a moderate agreement. On the other hand, the weighted kappas were 0.64 and 0.74 meaning good agreement between the two systems. Indeed, weighting gives more importance to disagreements beyond two contiguous categories (e.g. ACR-TIRADS 3 becomes EU-TIRADS 5) and reduces the share of minimal disagreements (ACR-TIRADS 4 becomes EU-TIRADS 5). In sum, the two systems have a good concordance and the disagreements mainly concern two adjacent categories, which does not dramatically modify the medical care.

This study suffered several limitations: It included 124 nodules, 39 of which were non-diagnostic specimens (Bethesda 1 category) that were excluded from most analyses. This relatively small sample presented a limit of our work. Also, the study included only nodules that validated the ACR-TIRADS 2017 criteria for thyroid FNNAC. As a result, nodules with a benign ultrasound appearance (cystic, spongiform etc.) and those whose size was below the thresholds set by the ACR were not included. This resulted in a selection bias and a high rate of malignancy in our sample of around 20%. This rate is higher than would be expected by the prevalence of thyroid cancer in the general population. The multitude of operators who performed cervical ultrasounds represented a limitation of our study and led to intra and interobserver variability in ultrasound evaluation of thyroid nodules. Furthermore, the standardized ultrasound report used in this work was based on the ACR-TIRADS 2017 criteria and did not specify accessory US features in the European classification such as intra-nodular Doppler vascularization and elastography rigidity. Finally, this study relied solely on cytological findings and final histological results were not available.

Conclusion

This study concluded that ACR and EU-TIRADS have equivalent diagnostic accuracy. It also concluded to an increasing malignancy risk with increasing TIRADS level. The agreement between the two systems is good and slight disagreements concerning two adjacent TIRADS categories will not have a considerable impact on subsequent medical management.

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