TIRADS score is of limited clinical value for risk stratification of indeterminate cytological results

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Abstract

Context: Thyroid nodules with cytological indeterminate results represent a daily and recurrent issue for patient management.

Objective: The primary aim of our study was to determine if TIRADS (Thyroid Imaging Reporting and Data System) could be used to stratify the malignancy risk of these nodules and to help in their clinical management. Secondary objective was to estimate if this risk stratification would change after reclassification of encapsulated non-invasive follicular variant of papillary carcinomas (FVPTC) as non-invasive follicular thyroid neoplasm (NIFTP).

Patients and methods: Single-center retrospective study of a cohort of 602 patients who were referred for ultrasound-guided fine-needle aspiration from January 2010 to December 2016 with an indeterminate cytological result and in whom histological results after surgery were available. TIRADS score was prospectively determined for all patients included. Nodules that had been classified as FVPTC were submitted to a rereading of histological report and reclassified as NIFTP when judged relevant. A table of malignancy risk crossing Bethesda and TIRADS results was built before and after this reclassification.

Results: The study included 602 cytologically indeterminate nodules. TIRADS score was positively correlated with the malignancy rate ($P < 0.0001$). Risk stratification with TIRADS was significant only in Bethesda V nodules ($P = 0.0004$).

However, the risk of malignancy in this Bethesda V category was always above 45%, whatever the TIRADS score.

Conclusion: For a clinician facing an indeterminate cytological result for a thyroid nodule, return to TIRADS score is of limited value in most conditions to rule in or rule out malignancy and to guide subsequent management of patients.

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Introduction

Cytologically indeterminate thyroid nodules represent a daily and recurrent issue for medical patient management. Nowadays, Fine Needle Aspiration Cytology (FNAC) is the most efficient tool to sort which nodules should be referred for surgery but cytological results remain indeterminate in 17–23% (1, 2).

The Bethesda System for Reporting Thyroid Cytopathology classifies indeterminate cytological results into 3 out of 6 categories: Bethesda III, Bethesda IV and Bethesda V with a respective rate of malignancy of 5–15, 15–30 and 60–75% (2). The Bethesda System and the American Thyroid Association guidelines integrate

recommendations (3, 4) regarding indeterminate thyroid nodules (repeated FNACs or surgery). The optimal strategy for such patients remains debated, being comprised between simple clinical and ultrasonographic surveillance, repeated FNA, core-needle biopsy, molecular testing, to partial or total diagnostic thyroidectomy. The difficulty relies in the complex equilibrium between underestimating and undertreating a thyroid cancer and over-treating a nodule that will be diagnosed as benign after histological analysis (5, 6, 7).

As the overall rate of malignancy in cytologically indeterminate thyroid nodules is low, the majority of patients should be managed conservatively. Ultrasound (US) could be useful to stratify the rate of malignancy. Various standardized systems were designed for accurate risk-stratification of thyroid nodules based on ultrasonographic features (1, 8, 9, 10). Our team created a system so called the French (TIRADS)Thyroid Imaging reporting and Data System, which was prospectively tested on 4550 nodules (1). The TIRADS system and another US risk stratification system designed by the American Association of Clinical Endocrinologists demonstrated a good correlation with cytological findings (9, 11). Previous studies have evaluated the impact of TIRADS scoring system on indeterminate cytological results management (5, 6, 7, 12). Their results were that TIRADS score could refine the malignancy risk assessment, suggesting a conservative approach for thyroid nodules with low risk of malignancy and a surgical approach for high risk ones. However, no standardisation is available and the assessment with the French TIRADS has never been studied for that purpose.

Approximately 85% of thyroid cancers are represented by papillary carcinomas (PTC) (13). Several variants of PTC have been described. The follicular variant of PTC (FVPTC) is the second most common subtype after the classic variant of PTC. The pitfall of indeterminate cytological results is mostly explained by the challenging diagnosis of follicular variant of papillary thyroid cancer (2). Moreover, recently the encapsulated non-invasive FVPTC has recently been reclassified as benign and renamed Non-invasive Follicular Thyroid Neoplasm with papillary-like nuclear features (NIFTP) (14) reducing the number of “true” thyroid cancers in indeterminate cytological results (15). On the opposite the most common subtype of PTC, namely the classical variant is easily diagnosed with FNAC.

The aim of our study was to stratify the risk of malignancy of indeterminate thyroid nodules (Bethesda categories III, IV and V) using a table crossing TIRADS and Bethesda, before and after reclassification of encapsulated

non-invasive FVPTC as NIFTP, and to analyse the clinical impact of such risk stratification.

Subjects and methods

Design and study

We conducted a single center retrospective study including all patients ($n=602$) with an indeterminate cytological results of a thyroid nodule FNAC performed between January 2010 and December 2016 for whom the results of a thyroid surgery with histological analysis (benign/malignant) was available.

US examination and TIRADS scoring

US Scanning was performed using a Toshiba Aplio MX scanner (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) and a Toshiba 500 with an electronically focused near-field linear probe at 8–14MHz bandwidth. All thyroid nodules were scored with the French TIRADS flowchart, already described by our team (1, 10).

TIRADS score ranged from 1 to 5. TIRADS 1 corresponded to a normal gland, TIRADS 2 to a cystic benign nodule or a spongiform one, TIRADS 3 to a highly probably benign nodule with no US features of suspicion. TIRADS 4A nodules were at low suspicion for malignancy and corresponded to a mildly hypoechoic nodule with oval shape, smooth margins and no microcalcifications. TIRADS 4B nodules were at high risk of malignancy, with one or two features of high suspicion among five: marked hypo-echogenicity, irregular margins, taller than wide shape, micro-calcifications, low elasticity. TIRADS 5 nodules were consistent with malignancy and harboured three or more features of high suspicion and/or a lymph node suspect of metastasis of thyroid origin.

Thyroid FNAC and cytological interpretation

FNAC was performed for all nodules using a capillary US-guided FNA technique and 27 G needles. In most of the cases, a single pass was performed per lesion for cytological analysis and all results were reported according to the Bethesda System (2, 3).

Indeterminate cytological results were classified as atypia of undetermined significance or follicular lesion of undetermined significance (Bethesda III), suspicious for a follicular neoplasm (Bethesda IV) and suspicious for malignancy (Bethesda V).

Bethesda category IV was subdivided into Follicular Neoplasm (FN) and Hürtle Follicular Neoplasm (HFN).

Histopathological results

All nodules were treated by surgery with histopathological results available in all cases. Matching of US-FNAC and histological data regarding nodules location and size was systematically checked. Malignancy risk crossing each TIRADS score and Bethesda result was first calculated according to the standard histological classification.

All histological reports of FVPTC were submitted to a rereading and characterized as invasive or encapsulated. Surgical specimens and slides were not analysed again. Those presenting all the following criteria were reclassified as NIFTP: encapsulation or clear demarcation, follicular growth pattern with no papillae, no psammoma bodies, no vascular or capsular invasion, no tumor necrosis, no high mitotic activity, no extra-thyroid invasion (15). Risk stratification of malignancy crossing TIRADS and Bethesda results was then performed again after reclassification of these nodules as NIFTP and therefore as benign.

Statistical analysis

Qualitative variables were described by frequencies and quantitative variables were described by their means and/or medians with variances and/or range. Student *t*-test was used to compare quantitative variables, and chi-square for qualitative variables. Non-parametric test such as Wilcoxon or Fisher test was used when usual tests were no longer appropriate.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each Bethesda category.

To model malignancy risk, we established a logistic regression. Univariate analysis was performed. Ascending selection was used to build the multivariate logistic regression model. To select factors, we performed a likelihood ratio test. Factors that obtained the most significant *P*-value were entered in the model until no more factors remains significant. A *P*-value <0.05 was taken to represent statistical significance. Statistical analysis was performed with R software, version 3.3.2.

Results

Demographic data and histological results

A total of 4357 nodules had an indeterminate cytological result according to the Bethesda classification after a FNAC performed during the period from January 2010

to December 2016. There was a majority of Bethesda III category (2381 nodules). Finally, the study included 602 indeterminate nodules (13.8% of 4357) with TIRADS score and histopathological data available (Fig. 1). Most nodules referred to surgery were of Bethesda IV and V categories (88.5%).

Demographics, US and histopathological characteristics are described in Table 1. The sex-ratio was 0.36 (M/F). The mean age of patients was 50.9 ± 14.8 years old. Regarding US features, TIRADS 4A was the most frequently reported score (69%). There were no TIRADS 1 or TIRADS 2 scores. The Bethesda IV classification was the main indeterminate cytological category observed (55.5%). Inside Bethesda IV, 246 were FN and 86 HFN. Histological analysis identified 392 benign cases (65.1%) and 210 malignant cases (34.9%). Among malignant cases, there were 175 PTC (83.3%), 17 follicular carcinomas (8.1%), and 18 other cases including intra-thyroidal metastasis from other organs and medullary carcinomas (8.6%). Inside the PTC group, 81 were FVPTC (46.2%). Among them, 23 FVPTC out of 81 were reclassified as NIFTP (28.4%).

The prevalence of thyroid nodules was lower in men but no difference was observed in the prevalence of malignant nodules according to gender (34 vs 35%, *P*=0.8). Subjects with malignant nodules were significantly younger (49 vs 52 y.o., *P*=0.02). Malignant risk was significantly correlated with nodule size (*P*=0.009). Nodules measuring above 4 cm had a tendency to be more frequently malignant (Supplementary data 1, see section on supplementary data given at the end of this article).

Figure 1

Flowchart of cytological distribution of thyroid nodules between 2010 and 2016.

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Table 1 Demographics and ultrasound characteristics of 602 patients. Data are presented as *n* (%) or mean $\pm$ S.D.

Characteristics	Value
Gender	
Women	444 (73.7%)
Men	158 (26.2%)
Age (years)	
≤ 40	145 (24.1%)
41–50	139 (23.1%)
51–60	161 (26.7%)
> 60	157 (26.1%)
TIRADS	
3	78 (13%)
4A	417 (69.3%)
4B	93 (15.4%)
5	14 (2.3%)
Bethesda	
3	69 (11.5%)
4	334 (55.5%)
5	199 (33.1%)
Histology	
Benign	392 (65.1%)
Malignant	210 (34.9%)
Histology	
Benign	392 (65.1%)
Classic PTC	94 (15.6%)
FVPTC	81 (13.5%)
Follicular carcinoma	17 (2.8%)
Other	18 (3%)
Nodule size (mm)	19.42 ($\pm$ 16.7)
Nodule size (cm)	
< 1	224 (41%)
1.1–2	114 (21%)
2.1–4	134 (24.5%)
> 4	74 (13.5%)

Comparison of TIRADS score, cytological and histopathological results

TIRADS score was positively correlated with histopathological results ($P < 0.0001$). The rate of malignancy increased according to US suspicion. The rate of malignancy was 21.5, 29, 63.4 and 100% in TIRADS 3, 4A, 4B and 5 respectively. TIRADS sensitivity, specificity, NPV, PPV and accuracy for the diagnostic of malignancy were 92.4, 15.8, 79.5, 58.8 and 42.5% respectively.

Bethesda III, IV and V were associated with a malignancy rate of respectively 23, 14 and 74% ($P < 0.0001$). Inside Bethesda IV, no significant difference was observed between FN and HFN as to malignancy rate.

Distribution of histological subtypes according to Bethesda and TIRADS scores are shown in [Table 2](#).

Nodules with highly suspicious US features ($\geq$ TIRADS 4B) were associated with the classical variant of PTC in more than 50% of cases (57.6%), whereas TIRADS 3 thyroid nodules were equally divided between the classical

variant and FVPTC. The majority of Bethesda III and Bethesda IV thyroid nodules were associated with FVPTC (56.3% and 50% respectively), whereas the majority of Bethesda V thyroid nodules were associated with classical PTC (54.7%).

The malignancy risk of indeterminate thyroid nodules using a table crossing TIRADS and Bethesda is shown on [Table 3](#).

There were 69 nodules classified as Bethesda III: 53 were benign (76.8%) and 16 malignant (23.2%). Among these, PPV of TIRADS was 15.79% for TIRADS 3, 25% for TIRADS 4A and 30% for TIRADS 4B. These differences did not reach statistical significance. TIRADS's sensitivity and NPV for the diagnosis of malignancy were 81.2 and 84.2%, respectively ([Table 3](#)).

There were 334 nodules classified as Bethesda IV: 288 were benign (86.2%) and 46 malignant (13.8%). Among these, PPV of TIRADS was 10.26% for TIRADS 3, 13.3% for TIRADS 4A and 25% for TIRADS 4B. There again, the differences did not reach statistical significance. TIRADS's sensitivity and NPV were higher in this Bethesda category compared to Bethesda III, 91.3 and 89.7% respectively ([Table 3](#)).

Finally, 199 nodules were classified as Bethesda V: 51 were benign (25.6%) and 148 malignant (74.4%). Among these, PPV of TIRADS was 45% for TIRADS 3, 70.7% for TIRADS 4A, 84.7% TIRADS 4B and 100% for TIRADS 5. Differences were statistically significant. TIRADS had a high sensitivity (93.9%) and PPV (77.6%) but a decreased NPV (55%). Malignancy rate was positively correlated with TIRADS score ($P = 0.0004$). TIRADS 5 was only found in Bethesda V category ([Table 3](#)).

The same analysis was conducted after reclassification of NIFTPs as benign tumors ([Table 4](#)). Among the 81 FVPTC, 23 were reclassified as NIFTPs (2 TIRADS 3, 21 TIRADS 4A). As shown in [Table 4](#), none of TIRADS 4B and 5 thyroid nodules were NIFTP. NIFTPs had low and intermediate risk US features (TIRADS 3 and 4A), but no high risk features. There was an improvement in TIRADS score risk stratification in each Bethesda category even if results remained not significant for Bethesda III and IV ([Table 4](#)).

Univariate logistic regression analysis was performed. Thyroid malignancy was significantly associated with an age below 55 ($P < 0.0001$), a nodule size larger than 4 cm ($P < 0.0001$), high TIRADS or Bethesda scores ($P < 0.0001$). Multivariate regression logistic analysis identified age, TIRADS score and Bethesda category as independent factors to predict malignancy risk ([Supplementary data 2](#)).

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Table 2 Histological subtypes of thyroid cancers according to Bethesda classification and TIRADS score.

Malignant histological subtypes	Bethesda			TIRADS			
	III	IV	V	3	4A	4B	5
Classical variant of PTC	3 (18.8)	10 (21.7)	81 (54.7)	7 (43.8)	45 (37.2)	34 (57.6)	8 (57.1)
FVPTC	9 (56.3)	23 (50.0)	49 (33.1)	7 (43.8)	54 (44.6)	17 (28.8)	3 (21.4)
Follicular carcinoma	3 (18.8)	7 (15.2)	7 (4.7)	2 (12.5)	11 (9.1)	4 (6.8)	0 (0.0)
Others	1 (6.3)	6 (13.0)	11 (7.4)	0 (0)	11 (9.1)	4 (6.8)	3 (21.4)

Discussion

Although FNA is the best simple and available test to differentiate malignant from benign thyroid nodules, its major limitation are indeterminate results, which account for 17% to 23% of all cases (2). In particular, FNA is not efficient to discriminate between follicular adenomas, FVPTC and FTC. The aim of our study was to determine if TIRADS scoring could provide a significant risk stratification of cytologically indeterminate nodules and guide clinical management.

Regarding Bethesda V category, there was a significant difference in the risk of malignancy among TIRADS scores, and TIRADS had a high sensitivity (93%). The clinical impact would be to advise for total thyroidectomy for nodules over 10mm or 20mm, if TIRADS score is greater than or equal to 4A. A simple lobectomy could be discussed in case of TIRADS 3 scores. But, finally, as the malignancy rate was never under 40%, even in TIRADS 3 nodules, surgery remains mandatory in all cases.

In Bethesda III and Bethesda IV nodules, no significant difference in the risk of malignancy between TIRADS scores was found in our series. Thus, TIRADS is of poor clinical help in these two Bethesda categories. Another way to look at it is to analyse the NPV of the TIRADS score. The only case in which NPV was below 10% corresponded to TIRADS 3-Bethesda IV nodules, which accounted only for 3 out of 602 cases. In all other Bethesda-TIRADS couples, NPV was over 10%, which seems insufficient

to allow managing patients with active surveillance in a secure way.

Other studies have depicted that US risk stratification could be useful for the management of cytological indeterminate results (5, 6, 7, 12). In the report by Maia *et al.* (5), a high NPV for nodules scored TIRADS 3 and 4A – Bethesda III (90%) and a high PPV of for nodules scored TIRADS 4B and 5– Bethesda V (76.9%) were found. However, in the same study, Bethesda IV thyroid nodules scored TIRADS 4B and 5 had a high PPV of 75%, (5) which differed from our PPV (25%). Bethesda IV rate of malignancy is known to be between 15–30% which is more consistent with our results (2). Regarding results of other studies some limitations have to be taken into account. Some evaluated the impact of TIRADS score on indeterminate cytological results without differentiating the subcategories of indeterminate nodules (6). Other studies clustered TIRADS into two groups: low or high suspicion for malignancy without assessing PPV of each TIRADS score (12). High PPV or NPV, which are not systematically informed (12), are essential component for a good stratification of malignancy risk. When looking at PPV and NPV, some studies did not find necessarily better values than ours (6).

The explanation of the lack of significance of TIRADS scoring in Bethesda III and IV categories could be linked to histological subtypes. We found 83.3% of PTC, which was in line with the known pathological spectrum of thyroid cancers (13). However, there was an ‘over-representation’

Table 3 Malignancy rate comparing Thyroid Imaging Reporting and Data System (TIRADS) score, cytological and histopathological results.

	TIRADS				P value
	3	4A	4B	5	
Bethesda III					0.6727
B	16 (84.21%)	30 (75%)	7 (70%)	0 (0%)	
M	3 (15.79%)	10 (25%)	3 (30%)	0 (0%)	
Bethesda IV					0.2417
B	35 (89.74%)	235 (86.72%)	18 (75%)	0 (0%)	
M	4 (10.26%)	36 (13.28%)	6 (25%)	0 (0%)	
Bethesda V					0.0004
B	11 (55%)	31 (29.25%)	9 (15.25%)	0 (0%)	
M	9 (45%)	75 (70.75%)	50 (84.75%)	14 (100%)	

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Table 4 Malignancy rate confronted to Thyroid Imaging Reporting and Data System (TIRADS) score, cytological and histopathological results after reclassification in Non-invasive Follicular Thyroid Neoplasm with papillary-like nuclear features.

	TIRADS				P value
	3	4A	4B	5	
Bethesda III					0.4707
B	16 (84.21%)	35 (87.5%)	7 (70%)	0 (0%)	
M	3 (15.79%)	5 (12.5%)	3 (30%)	0 (0%)	
Bethesda IV					0.0824
B	36 (92.31%)	243 (89.67%)	18 (75%)	0 (0%)	
M	3 (7.69%)	28 (10.33%)	6 (25%)	0 (0%)	
Bethesda V					<0.0001
B	12 (60%)	39 (36.79%)	9 (15.25%)	0 (0%)	
M	8 (40%)	67 (63.21%)	50 (84.75%)	14 (100%)	

of FVPTC (46.3% of PTC vs 27% expected) (13). Our study confirms previous ones which found that the proportion of indeterminate cytological results in FVPTC was higher than in conventional PTC (16). This may be explained by the fact that vascular or capsular invasion which are the key criteria for distinguishing follicular adenomas from follicular thyroid carcinomas or FVPTC cannot be detected in cytological samples. FVPTC and FTC has been reported to frequently have a US benign appearance contrary to classical variant of PTC (16, 17, 18, 19). We found the same result: 75.5% of FVPTC and FTC were TIRADS 3 or TIRADS 4A. This could explain the non-significant result of TIRADS stratification for malignancy risk in these two categories. TIRADS scoring may be less efficient for malignancy risk assessment of FVPTC than for the classical variant. On the other hand, TIRADS enabled a stratification of malignancy risk inside Bethesda V category, which corresponded mainly to the classical variant of PTC.

However, encapsulated FVPTC without capsular or vascular invasion has been shown as bearing a very low risk of adverse outcome (20, 21). This recently conducted to a reclassification of this histological subtype in benign tumours called NIFTP (14, 15). Because of the high prevalence of FVPTC in our indeterminate cytological results we conducted a new evaluation after NIFTP reclassification as benign nodules. This new classification improved TIRADS impact on detecting malignant nodules. None of TIRADS 4B and TIRADS 5 thyroid nodules were NIFTPs. Only TIRADS 3 and 4A nodules were concerned with NIFTP reclassification. This reclassification allowed to decrease the percentage of malignant nodules in TIRADS with low suspicion US features (TIRADS 3 and 4A) and consequently to increase the NPV of TIRADS 3 and 4A (86% and 90% respectively).

Facing thyroid nodules with indeterminate cytological results, other options can be valuable to

increase diagnostic accuracy: repeated FNAC, iodine 123 scintigraphy, core needle biopsy, immunocytochemistry, molecular testing (22, 23). In Ratour *et al.* study, no benign immunocytochemistry results were associated with a malignant lesion (24). Molecular profiling could be of great contribution to indeterminate FNAC diagnosis (25), but it is not available in all countries, like France. Moreover, the cost-effectiveness of these tests is disputable.

There are several limitations to our study. The first one could be a possible selection bias due to the retrospective nature of the study. Second, indication for surgery was not taken into account. As a consequence, there is an over representation of Bethesda V which are more often subjected to surgery than Bethesda III or Bethesda IV nodules are. This explains the higher rate of thyroid cancer in our study (2, 3, 4, 8). The absence of statistical significance of TIRADS for risk stratification of Bethesda III nodules could also be due to a lack of statistical power: the limited number of Bethesda III, TIRADS 4B and 5 cases could increase the risk of type II (beta) statistical error. Another limitation is related to the lack of new rereading of surgical specimens and slides to reclassify cancers as NIFTP. However, systematic in-depth macroscopic and microscopic studies were conducted in our expert center with particular care to capsular analysis, which limits the risk of wrong reclassification.

In conclusion, a high global sensitivity in detecting malignancy (92.4%) was found for TIRADS in cytologically indeterminate nodules. However, by analysing the impact of TIRADS score for each Bethesda category, a positive association between malignancy risk and TIRADS score was significant only in Bethesda V. These results are in contradiction with other studies, which have depicted that US risk stratification could be useful for the management of cytological indeterminate results. TIRADS NPV was insufficient in most cases to allow avoiding surgery and be used as a rule out test. On the contrary, the high PPV

of malignancy for TIRADS 4B and 5 may suggest a surgical approach whatever the Bethesda category. Regarding Bethesda V nodules a surgical approach is recommended regardless of the TIRADS score. The weakness of TIRADS score to rule in malignancy in indeterminate cytology mainly appears to be related to the high proportion of FVPTC, which often has no US features of high suspicion. Future studies could investigate whether other US features, such as the halo, composition and vascularity, can increase the diagnostic accuracy of FVPTC and follicular carcinoma.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-18-0078>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Clinical Study	E Chaigneau and others	TIRADS score impact on indeterminate nodules	179:1	20
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