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RESEARCH

Risk of TIRADS-based inappropriate FNAC in autonomous thyroid nodules is clinically negligible

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Abstract

Objective: Thyroid nodule (TN) is usually managed according to Thyroid Imaging And Reporting Data Systems (TIRADS) with the major aim to reduce as much as possible unnecessary fine-needle aspiration cytologies (UN-FNACs). Since the assessment of autonomously functioning thyroid nodule (AFTN) according to TIRADS is heterogeneous, that virtually benign entity may increase the rate of UN-FNAC. This study retrospectively analyzed the appropriateness of TIRADS-based FNAC indication in AFTNs, also looking at the impact of TSH and nodule size.

Methods: Cases diagnosed with AFTN on scintigraphy were searched. Patients who had undergone AFTN treatment, were on medications or supplementation that could affect thyroid function, or had multiple AFTNs were excluded. The AFTNs were assessed according to ACR-TIRADS.

Results: Forty-eight AFTNs were included of which 37.5% had FNAC indication according to TIRADS. The FNAC indication rate in the case of TSH lower than 0.4 mIU/L was significantly higher than in other cases ($P = 0.0078$). The most accurate TSH cut-off and AFTN size associated with UN-FNAC were ≤ 0.41 mIU/L and > 22 mm, respectively. The multivariate analysis showed that both TSH and nodule size were independent predictors of UN-FNAC with OR of 6.65 and 6.46, respectively. According to these data, the rate of FNAC indication dropped to 4.16%.

Conclusion: Inappropriate FNACs in AFTNs are primarily observed in patients with low TSH and large AFTN. Since these cases typically undergo scintigraphy, the risk of TIRADS-based UN-FNAC is clinically negligible. There is no need for integrating other imaging procedures into the TIRADS model.

Keywords: autonomous; FNAC; thyroid; TIRADS; ultrasound

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Introduction

Thyroid nodule (TN) is a common pathological condition requiring a specific diagnostic workup (1). The first step in diagnosing thyroid disorders is to conduct a physical examination of the thyroid gland, followed by laboratory tests and a neck ultrasound, if necessary. Thyroid function tests, such as TSH measurement, are used to assess thyroid function, while ultrasound can help to determine the risk of malignancy of any detected lesions. This diagnostic process is highly reliable and recommended by thyroid experts (2, 3). Over the past decade, Thyroid Imaging and Reporting Data Systems (TIRADS) have achieved wide global adoption (4). One of their primary objectives is to standardize the lexicon used in thyroid ultrasound reports. They also aim to improve the indication of fine-needle aspiration cytology (FNAC) by evaluating TNs based on category-risk assessment and category-specific dimensional cut-offs. Although the different TIRADS were developed with varying geographical and cultural contexts in mind, their accuracy has been demonstrated to be high enough to reduce the need for other imaging procedures over time (5). The reliability of TIRADS can be measured by the rate of unnecessary FNAC (UN-FNAC), which refers to biopsies that yield a final benign cytological/histological outcome. The lower the rate of UN-FNAC, the higher the reliability of TIRADS (6).

Autonomously functioning thyroid nodule (AFTN) is a thyroid nodule that can produce hormones independently of the body's needs. While hyperplasia and neoplasm can occur in AFTNs (7), they are typically considered benign despite rare reports of malignant AFTNs (8, 9), and FNAC is not usually recommended (2, 3). However, since AFTNs have a heterogeneous ultrasound appearance and are generally larger than the TIRADS category-specific size (10, 11, 12), they can increase the number of UN-FNACs and potentially lead to unnecessary diagnostic surgery (13). Since thyroid scintigraphy (TS) is still recognized as the gold standard for detecting AFTN, authors suggested integrating TS in the TIRADS model to prevent UN-FNACs (10, 12, 13). However, the TIRADS-based strategy was proven highly accurate and guidelines recommend TS only in TN patients with suspicious subclinical hyperthyroidism (i.e. TSH levels lower than 1.0 mIU/L) (2, 3).

This study aims to evaluate the appropriateness of TIRADS-based FNAC indications in patients with TS-proven AFTN. It retrospectively analyzes a series of AFTNs using ACR-TIRADS (14) and calculates their indication for FNAC. The study also explores the impact of major clinical data, such as TSH levels and nodule size.

Materials and methods

Institutional context and flow of thyroid nodule patients

Our institution is the major healthcare organization in Tessin Canton and comprises four regional hospitals. The institutional service of endocrinology is present in all these hospitals. Ours is a major nuclear medicine service in the canton. Patients with thyroid nodules diagnosed by non-thyroid specialists are generally referred to our endocrinology service. In addition, patients with large multinodular goiters may be referred by their general practitioners for TS with the aim of ruling out AFTN regardless of TSH levels. Since our database includes patients undergoing both thyroid ultrasound and scintigraphy, this institutional context represents a good setting to explore retrospective series of AFTN and thus meet the aim of the study.

Case selection

Our endocrinology clinic's database was searched to retrieve patients diagnosed with AFTN who were seen at our center between January 2019 and March 2024. We included cases with a confirmed AFTN diagnosis through TS and available data on thyroid ultrasound and laboratory tests. Patients who had undergone AFTN treatment (such as surgery, radioiodine, and thermal ablation) before our visit, were on medications or supplements that could affect thyroid function (such as thyroid hormones, anti-thyroid drugs, amiodarone, and iodine), or had multiple AFTNs were excluded from the study.

Measures

One expert radiologist (AL) and one expert endocrinologist (PT) reviewed the ultrasound images of the selected patients to classify the AFTNs using the 5-tiered ACR-TIRADS (American College of Radiology Thyroid Imaging Reporting and Data System) classification system, which ranges from TR1 (benign) to TR5 (highly suspicious) (14). According to ACR-TIRADS, FNAC is indicated in cases of nodules ≥ 1 cm and assessed as TR5, or ≥ 1.5 cm and TR4, or ≥ 2.5 cm and TR3 (14). In addition, ACR-TIRADS recommends follow-up of nodules assessed as TR5 and sized 0.5–1 cm, or TR4 and sized 1–1.5 cm, or TR3 and sized 1.5–2.5 cm. The inter-observer agreement between the two raters was previously known as very good because of their strict collaboration in clinical activity. The present series of AFTNs represents a part of a larger series of thyroid nodules that were independently reviewed by the two raters for study purposes. Thus, when the two raters re-assessed the nodules included in the present study, they were not aware that the lesions were AFTNs. In any case, their inter-observer variation in the present series was 6.25%, and the discrepant cases were resolved in a meeting.

The FNAC indication was established based on the ACR-TIRADS category and the category-specific dimensional threshold. As the present study was a retrospective analysis, the results were independent of the indication for FNAC in real life during clinical practice. Data of TSH (and free-T3/free-T4) were extracted from patient's

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records. In patients with multiple TSH evaluations, the lowest TSH value was considered.

Thyroid tests were performed with chemiluminescence immunoassay technology. Their normal ranges in clinical practice are the following: TSH between 0.40 and 4.0 mIU/L, free-T3 between 3.8 and 6.8 pmol/L, and free-T4 between 12 and 22 pmol/L.

Statistical analysis

The manuscript reported the results of continuous parameters as the median and interquartile range (IQR). The Mann–Whitney *U* test was used to compare continuous parameters from subgroups. The Pearson test was used to analyze the correlation between continuous parameters. The frequency of dichotomous parameters from subgroups was compared using the Fisher or Chi-square test. A lesion-based analysis was used to determine the performance of ACR-TIRADS in assessing AFTNs and indicating FNAC. The ROC curve analysis was used to analyze the influence of TSH value and AFTN diameter on ACR-TIRADS, calculating the area under the curve (AUC) and identifying the best cut-off point and its related sensitivity and specificity with a 95% confidence interval (95% CI). A multivariate logistic regression analysis was performed to identify independent predictors of UN-FNAC. The Odds Ratios (OR) with 95% CI were used to estimate the association between variables and UN-FNAC. The statistical significance level was set at $P < 0.05$. The statistical analyses were performed using GraphPad Prism version 7 or MedCalc (MedCalc Software Ltd, Belgium).

Ethics

The protocol of this retrospective study was approved by the Ethics Committee of Cantone Ticino. Accordingly, patients gave informed consent for their inclusion. All procedures comply with the 1964 Helsinki Declaration.

Results

Patient features

Based on the predefined selection criteria, the study included 48 patients with single AFTN, of which 89.6% were female. The median age of the patients was 63 years, and the median size of the AFTN was 21 mm. Of these patients, 28 (58.3%) had TSH lower than the lower reference limit (LRL) (ranging from 0.005 to 0.39 mIU/L), with 15/28 (53.6%) having suppressed TSH levels, while the remaining 20 (41.7%) had normal TSH values (ranging from 0.41 to 2.3 mIU/L). One patient had free-T3 levels higher than the upper reference limit, and the other five patients had free-T4 levels higher than the upper reference limit. No patients underwent FNAC during real clinical practice. The study series is described in detail in Table 1.

TIRADS assessment

Based on the ACR-TIRADS classification system, out of 48 AFTNs, 2 (4.16%) were considered TR5, 9 (18.75%) TR4, 27 (56.25%) TR3, and 10 (20.83%) TR2. Regarding the two TR5 nodules, one was sized 21 mm and was very hypoechoic with irregular margins and peripheral (rim) calcification, while the second one had a major diameter of 8 mm and was solid hypoechoic. The ACR-TIRADS assessment identified that 18 (37.5%) cases required FNAC, while 8 (16.7%) cases required follow-up. Figure 1 illustrates the distribution of the 48 AFTNs across the ACR-TIRADS, with or without FNAC indication and based on normal or low TSH levels.

Analysis of TSH and AFTN's size

Figure 2 illustrates the distribution of AFTN with and without FNAC indication based on their major diameter and TSH levels. The TSH value of patients with an indication for FNAC (median: 0.13 mIU/L, IQR: 0.009–0.32) was found to be significantly lower ($P = 0.0097$) than those of patients without FNAC indication (0.49 mIU/L, IQR: 0.10–0.76). Even though the ACR-TIRADS assessment was not significantly different between the subgroups of patients with TSH lower than 0.4 mIU/L or normal TSH ($P = 0.41$) (Fig. 1), the rate of FNAC indication was significantly ($P = 0.0078$) higher in the former (15/28, 53.6%) than in the latter (3/20, 15%) (Fig. 2). The ROC curve analysis of TSH revealed that the most accurate cut-off point to predict UN-FNAC was ≤ 0.41 mIU/L with 88.9% (65.3–98.6) sensitivity and 54.5% (32.2–75.6) specificity (AUC: 0.66, 95% CI: 0.50–0.81). The nodule size was inversely correlated with TSH levels ($P = 0.037$), as shown in Fig. 3. The major diameter of the AFTNs of patients with TSH levels below the LRL (25.0 (15.5–31.8) mm) was higher but not significantly different ($P = 0.11$) from that of patients with normal TSH (19.5 (14.8–23.8) mm). The ROC curve analysis of AFTN diameter revealed that a diameter > 22 mm was the most accurate threshold to predict UN-FNAC. This threshold showed a sensitivity

Table 1 Characteristics of the study series. Data are presented as median (IQR).

Variable	Values
Sex (female/male), *n*	43/5
Patient's age (years)	63 (53.7–72)
AFTN major diameter (mm)	21 (15.5–30.7)
TSH (mIU/L)	0.31 (0.032–0.70)
Free-T3 (pmol/L)	4.9 (4.1–5.2)
Free-T4 (pmol/L)	15.6 (13.7–18.5)

AFTN, autonomously functioning thyroid nodule; IQR, interquartile range.

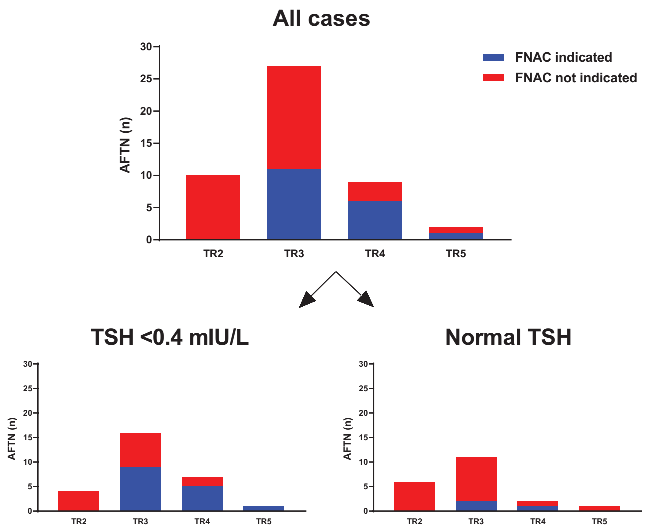

Figure 1

Results of the assessment of AFTNs across the ACR-TIRADS also consider the TSH value. AFTN, autonomously functioning thyroid nodule; TR is the ACR-TIRADS risk category: TR1, benign; TR2, not suspicious; TR3, mildly suspicious; TR4, moderately suspicious; TR5, highly suspicious.

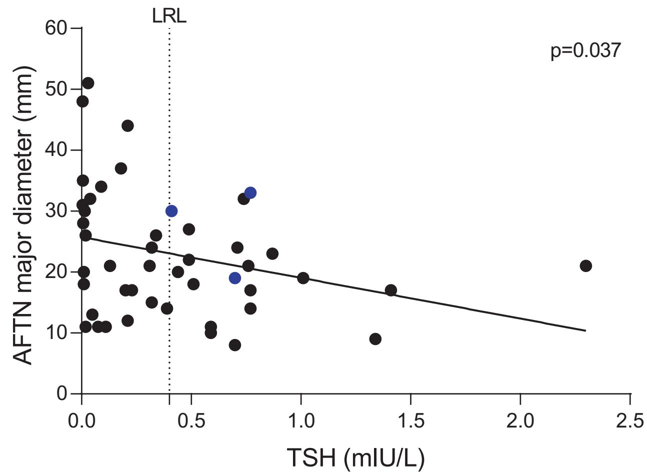

Figure 3

Correlation between TSH and AFTN size. AFTN is an autonomously functioning thyroid nodule; LRL has a lower reference limit. The three blue dots indicate the AFTNs of patients with normal TSH who have an FNAC indication according to ACR-TIRADS.

of 72.2% (46.5–90.3) and a specificity of 77.2% (54.6–92.2) with an AUC of 0.79 (95% CI: 0.63–0.90).

Multivariate analysis

The multivariate analysis, including the ROC-derived best cut-off of TSH and AFTN size, showed that both were independent predictors of UN-FNAC with OR: 6.65 (95% CI: 1.08–40.76, $P = 0.040$) and 6.46 (95% CI: 1.39–29.95, $P = 0.017$), respectively.

Re-evaluation of FNAC indication according to TSH and size

The indication for FNAC might be revised based on TSH levels and AFTN size. If TSH levels are lower than LRL and indicate TS rather than FNAC (2, 3), the rate of FNAC indication in the entire population decreased to 6.25% (3/48). According to the ROC-derived TSH best cut-off, the rate of FNAC indication is 4.16% (2/48). In addition, the frequency of FNAC indication in patients with AFTN smaller than the ROC-derived dimensional threshold was 18.51% (5/27).

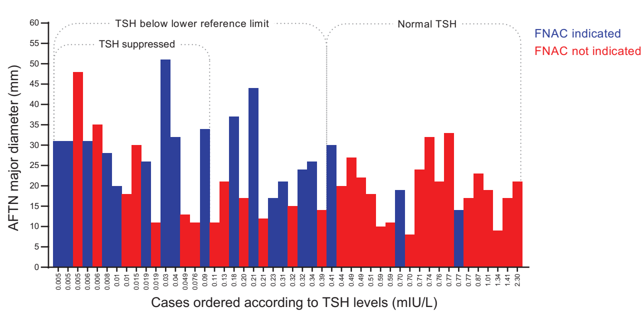

Figure 2

Distribution of AFTN with or without FNAC indication according to nodule's size and TSH value. AFTN, autonomously functioning thyroid nodule; the lower reference limit of TSH is 0.40 mIU/L.

Discussion

The impact of TIRADS in clinical practice has been significant. With the advent of these systems, it has been shown that we can adopt a TIRADS-based strategy to manage goiter patients with high accuracy. However, it is important to consider that TIRADS was designed to detect papillary thyroid carcinoma in ultrasound images (15). Therefore, it may not be as effective in detecting other types of cancer or benign lesions (16, 17). In particular, benign lesions like AFTNs may be wrongly identified as cancerous using TIRADS, leading to possible inappropriate FNAC testing (10, 11, 12, 13). To address this issue, the present study was conducted in order to investigate the rate of inappropriate FNAC in AFTNs based on TIRADS guidelines.

More than three-quarters of the AFTNs were assessed as benign/mildly suspicious (i.e. TR2 or TR3), according to ACR-TIRADS. This is initially reassuring because most AFTNs do not require FNAC testing. However, FNAC was indicated in about one-third of AFTNs according to TIRADS recommendations.

The study also found a correlation between TSH levels and AFTN size. This was expected as it is well recognized that the larger the AFTN volume, the higher its inappropriate hormonal production. Furthermore,

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the analysis showed that specific subgroups of patients had significantly different rates of UN-FNAC. Patients with normal TSH levels and patients with smaller AFTNs had a lower rate of FNAC indication. According to the present findings, a clinically oriented discussion can be addressed.

First, most literature on TIRADS evaluates TN outside the clinical context of patients. This is often due to retrospective studies analyzing cases that have undergone FNAC, histology, or other standards. TIRADS are solely recommendations based on ultrasound characteristics of TN. In AFTN, TS is the reference, recommended for patients with suspected (subclinical) hyperthyroidism in nodular goiter, highlighted by low/very low TSH levels (2, 3). This actually affects studies on inappropriate FNAC in AFTNs. These studies (10, 11, 12, 13) (Table 2), including the current one, correlated ultrasound and scintigraphic data in cases undergoing TS for various reasons (over/subclinical hyperthyroidism, suppressed/low/normal TSH, AFTN suspicion, nodular goiter assessment). However, these retrospective analyses are prone to selection bias and provide theoretical data on FNAC indications for cases actually requiring different management. When dealing with nodular goiter and TSH below the LRL, endocrinologists focus more on hyperthyroidism than TN nature, often recommending TS immediately after ultrasound. Thus, thyroid functional test results are part of the evaluation of the rate of unnecessary FNAC in AFTNs, as this study shows. Moreover, the size threshold for FNAC varies across TIRADS and is debatable (4, 14, 18, 19). The cut-off size for FNAC has yet to be definitively established. Whether to apply the TIRADS dimensional thresholds for each risk category is currently being evaluated (20, 21, 23). Our study shows decreased unnecessary FNAC in smaller lesions when AFTN size is fully considered. This correlation is pivotal as most AFTNs are classified as low-to-intermediate risk by ACR-TIRADS, with higher size thresholds for FNAC compared to high-risk categories. Notably, one study (10) used Kwak-TIRADS that advocates for FNAC in TNs classified 4A or higher, regardless of their size (22). Therefore, considering TSH and nodule size as independent predictors of unnecessary FNAC in AFTNs, we can recommend TS for patients with TSH below the LRL and follow TIRADS for FNAC in other cases. This clinically oriented strategy minimizes the risk of unnecessary FNAC in AFTNs, enabling efficient detection of clinically relevant cases.

Second, performing FNAC in AFTNs may result in indeterminate reports (i.e. Bethesda III or IV), complicating their management. The prevalence of cancer in patients with toxic nodular goiter is generally estimated at up to 9%, similar to euthyroid multinodular goiter (24). Rare malignant AFTNs have also been reported (8, 9). Thus, FNAC should remain indicated for AFTNs classified as high risk by TIRADS. Surgery is, in any case, an option for treating AFTN (25) and hot indeterminate lesions (2, 3).

Third, performing TS before potentially unnecessary FNAC is controversial (10, 11, 12, 13). Modern medicine emphasizes reducing the costs of inappropriate/unnecessary diagnostic procedures. TIRADS performance is often evaluated by the rate of

Table 2 Characteristics and general results of the previous studies and the present one.

	Schenke *et al.* (10)	Castellana *et al.* (11)	Noto *et al.* (12)	Kyrilli *et al.* (13)	Present study
AFTN					
Cases, n	615	87	51	66	48
Size, mm	23.2	22	17	27	21
Patient					
Age, years	58.3	61	54	56.3	21
TSH, mIU/L	0.56	0.27	1.20	0.41	0.31
ACR-TIRADS assessment, %					
TR1	–	11.5	17.6	–	0
TR2	–	5.7	17.6	–	20.8
TR3	–	49.4	33.5	–	56.3
TR4	–	32.2	27.5	–	18.8
TR5	–	1.2	3.9	–	4.1
FNAC indicated by TIRADS, %					
Kwak-TIRADS	83.5*	–	–	86.6**	–
ACR-TIRADS	–	44.8	25.5	–	37.5
EU-TIRADS	–	60.9**	43.1**	–	–
K-TIRADS	–	88.9**	–	–	–

AFTN size, patient's age, and TSH levels are reported as mean (10, 13) or median (11, 12).
[a]Kwak TIRADS (18) recommends indicating FNAC in nodules assessed as 4A category or higher; [b]EU-(19) and K-TIRADS (20) recommend FNAC according to lower dimensional cut-offs than the ACR-TIRADS.
AFTN, autonomously functioning thyroid nodule.

unnecessary FNAC (5). However, routinely applying TS to reduce unnecessary FNAC is not cost-effective due to TS costs. Data from Noto *et al.* (12) highlighted that among 449 patients undergoing TS, 81 AFTNs were identified, with a negligible prevalence of AFTN among TNs requiring FNAC (up to 7.6%) regardless of the TIRADS used. This issue may warrant discussion depending on the geographical context and AFTN incidence (26).

Lastly, this study indirectly confirms the variability of TIRADS assessments (4). Different systems have been developed in varied cultural settings (5). Our data, along with previous studies (10, 13), contribute to creating an international TIRADS (I-TIRADS) (27).

The study's limitations include its retrospective nature, potential selection bias, and small sample size, though they are comparable to other studies in the field. The retrospective re-assessment of static ultrasound images of AFTNs available in RIS-PACS can be seen as a potential bias. In particular, the finest ultrasound features, such as hyperechogenic spots or lobulations, may not be recognized in static images. However, in agreement with the largest part of the 25-year literature about ultrasound in thyroid nodules, the present study design should be the most adequate. It is reassuring that, even if the two ultrasound raters had a good inter-observer agreement, the study design included that eventual discordant cases would have been resolved in a final mutual meeting to achieve a consensus. However, this study uniquely examines UN-FNAC in AFTN, considering clinical data such as TSH levels and nodule size crucial for FNAC recommendations. Derived from clinical practice in a thyroid unit, the results are broadly applicable.

In conclusion, our results collectively state that AFTNs may undergo unnecessary FNAC according to TIRADS recommendations. The novel finding is that inappropriate FNACs in AFTNs are primarily observed in patients with TSH below the LRL and/or large AFTN size. Since these cases typically undergo TS before further examinations, the risk of inappropriate TIRADS-based FNAC in AFTNs is negligible. Therefore, integrating scintigraphy into the TIRADS model is unnecessary. This information is useful in the development of I-TIRADS.

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

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