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RESEARCH

Analysis of FNAC indication in thyroid nodules assessed as low risk according to various TIRADSs

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Abstract

Background: Thyroid nodule (TN) is a common entity, and TNs assessed by Thyroid Imaging and Reporting Data Systems (TIRADSs) as low-risk lesions (TIRADS 3) can significantly impact the rate of unnecessary biopsy (UN-FNAC). This study reviewed a consecutive series of patients undergoing surgery to analyze TNs assessed as TIRADS 3.

Methods: Thyroid surgeries performed from January 2019 to August 2024 were reviewed. Patients with preoperative thyroid ultrasound were selected, and TNs were classified according to American College of Radiology (ACR), European Thyroid Association (EU), and Korean (K) TIRADS. Cases assessed as TIRADS 3 were finally included. Histology was the reference standard to calculate the rate of UN-FNAC.

Results: The study series included 284 TNs assessed as TIRADS 3. The risk of malignancy was 8.7% in ACR-, 10.7% in EU-, and 10.1% in K-TIRADS, higher than expected. The frequency of TNs with indication for biopsy according to K-TIRADS (66.7%) was significantly (P = 0.003) higher than ACR-TIRADS (46.7%), with an intermediate value of EU-TIRADS (56.5%). The percentage of cancers with indication for biopsy according to ACR-, EU-, and K-TIRADS was 25%, 50%, and 50%, respectively. The overall rate of UN-FNAC was 95.3% in ACR-TIRADS, 90.3% in EU-TIRADS, and 92.4% in K-TIRADS.

Conclusion: How to save on UN-FNACs in low-risk TNs is challenging. Although ACR-TIRADS can be effective in reducing the total number of biopsies, the rate of UN-FNAC remains significant. Alternative strategies should be developed.

Keywords: thyroid; ultrasound; TIRADS; low risk; unnecessary FNAC

Introduction

As thyroid nodule (TN) is a common disease with an expected low frequency of cancer, consistent rule-out strategies to use in clinical practice are needed (1). Although fine-needle aspiration cytology (FNAC) of TNs represents the gold standard to detect and exclude cancers before surgery, performing FNAC in the huge number of

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TNs is not a cost-effective and thinkable strategy. Instead, ultrasound (US) evaluation is universally recognized as highly reliable in assessing the risk of malignancy (RoM) of TNs and then suggesting or not suggesting FNAC (1). In addition, US is a safe imaging procedure, widely used as an in-office evaluation alongside the endocrinological visit. For these reasons, important international societies developed US-based risk-classification systems, namely Thyroid Imaging Reporting and Data System (TIRADS) (2, 3, 4, 5), with the intention to i) facilitate TN risk assessment by US operators and ii) improve the selection of TNs for FNAC. The high performance of the TIRADSs has been largely demonstrated in the literature. They have comparable ability in stratifying the RoM of TNs (6), with slight differences in saving unnecessary FNAC (i.e., UN-FNAC) (7, 8), defined as FNAC performed in TNs with benign/not neoplastic outcome (i.e. category II of the Bethesda system (9)).

Considering the huge number of patients with (multi) nodular goiter, and in view of the rule-out strategy recommended by international societies, the analysis of UN-FNAC among ultrasonographically low-risk TNs seems more important. In fact, while the very low-risk/benign categories (ACR-, EU-, or K-TIRADS 1–2) do not require FNAC, and the impact of UN-FNAC can be negligible among TNs assessed as high risk (TIRADS 5) or intermediate risk (TIRADS 4), the case of the low-risk category (TIRADS 3) is much different. These nodules present as partially cystic or isoechoic without any of the worrisome features, with an estimated RoM much lower than that of TIRADS 4 and 5 (3, 4, 5). As the incidence of TNs assessed as TIRADS 3 in clinical practice is important (10), this category represents the major burden of UN-FNACs in any institution. Thus, reducing FNACs in TNs assessed as ACR-, EU-, or K-TIRADS 3 could contribute to improving the rule-out strategy needed to face the huge quantity of goiter patients. This issue also achieves high interest in the perspective of the project aimed at developing a unique international TIRADS (I-TIRADS), endorsed by major societies (11).

The present study was undertaken to challenge the TIRADS indication for FNAC in a series of TNs ultrasonographically assessed as low risk (TIRADS 3). As it is presumed that the largest part of these cases is benign, with the intent to fully explore the matter, a consecutive series of patients undergoing surgery and histology was employed. Major US classification systems, such as ACR-, EU-, and K-TIRADS (3, 4, 5), were considered.

Methods

Local setting

Our institution represents the highest-volume organization in the field of thyroid disorders in Tessin Canton, with the highest number of thyroid surgeries in this region. Cases with a possible indication for surgery are usually discussed in the institutional multidisciplinary meeting coordinated by the institutional Thyroid Unit. Most patients undergoing thyroid surgery are submitted to thyroid US, and images and clips are stored in the RIS-PACS.

Case selection

The study includes patients undergoing thyroid surgery from January 2019 to August 2024. Thyroid cancers were classified as papillary (PTC), follicular (FTC), or medullary (MTC) thyroid carcinoma and staged according to the current TNM edition. The study design included a five-step procedure: i) adults undergone thyroid surgery for all causes were searched in the institutional database; ii) cases with available preoperative thyroid US images in RIS-PACS were selected; iii) TNs with a diameter of at least 10 mm were classified across the categories of ACR-, EU-, and K-TIRADS (3, 4, 5) by an expert radiologist (AL), blinded to the final histological diagnosis; iv) cases assessed as TIRADS 3 of the three systems were included in the study; v) TIRADS data and corresponding histological diagnoses were aligned by an expert endocrinologist (PT). Cases of disagreement were discussed until mutual consensus was reached. The above protocol was chosen to use histology as the reference standard and then avoid FNAC-associated possible biases.

Ethics

The study protocol was approved by the Ethics Committee of Tessin Canton (Switzerland). Accordingly, patients gave written informed consent for inclusion. All procedures comply with the 1964 Helsinki Declaration.

Statistical analysis

Histology was the diagnostic gold standard. The indication for FNAC was assessed according to the recommendations of the three TIRADSs (3, 4, 5). The rate of UN-FNAC was calculated as follows: histologically proven benign TNs with indication for FNAC/TNs with indication for FNAC. Cancers were staged according to current histological classification systems, and their risk of relapse was assessed according to the risk stratification system of the American Thyroid Association (12). Continuous parameters were treated with non-parametric statistics. The comparison of frequencies was analyzed using the chi-square test. Statistical significance was set at $P < 0.05$. Analyses and figures were performed with GraphPad Prism version 7 (GraphPad software, USA).

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Table 1 Features of cases included in the study and main results.

	Guideline features		Study case							
			TN and cancer					Indication for FNAC		
	Estimated RoM	TN's size to indicate FNAC	TNs, *n*	Cancer rate	FTC	PTC	Relapse risk	Cases, *n* (%)	FTC	PTC
ACR-TIRADS 3	2.1–5%	>2.5 cm	92	8.7%	2	6	8 LR	43 (46.7%)	2 LR	
EU-TIRADS 3	2–4%	>2.0 cm	93	10.7%	3	7	1 IR; 9 LR	52 (56.5%)	3 LR	2 LR
K-TIRADS 3	3–10%	>2.0 cm	99	10.1%	3	7	1 IR; 9 LR	66 (66.7%)	3 LR	2 LR

RoM, risk of malignancy estimated in the guidelines; FNAC, fine-needle aspiration cytology; TN, thyroid nodule; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; LR, cancer at low risk of relapse; IR, cancer at intermediate risk of relapse.

Results

Case study

One hundred eighty-two patients operated during the study period were screened. Among them, TNs assessed as ACR-TIRADS 3 (n = 92), EU-TIRADS (n = 93), or K-TIRADS (n = 99) were selected; there were 8 (8.7%), 10 (10.7%), and 10 (10.1%) cancers, respectively. The median TN size was 25 mm in the ACR-TIRADS series, 25 mm in the EU-TIRADS series, and 25 mm in the K-TIRADS series. The cancer characteristics are detailed in Table 1.

TIRADS assessment

Both the number of cases assessed as TIRADS 3 and the cancer rate were not significantly different among the three systems. There were two cancers assessed as EU- and K-TIRADS 3 that were classified as TIRADS 4 according to the ACR system and then not included in the case series of the latter. Overall, the expected RoM of category 3 in the three TIRADSs (see Table 1) was not confirmed, the observed value being higher than that reported in the guidelines.

TIRADS indication for FNAC

The total frequency of TNs with indication for FNAC according to ACR-, EU-, and K-TIRADS was 46.7, 56.5, and 66.7%, respectively. The rate of FNAC indication according to K-TIRADS was significantly higher than that of ACR-TIRADS (P = 0.003), with no further differences between TIRADSs. The percentage of cancers with indication for FNAC according to ACR-, EU-, and K-TIRADS was 25, 50, and 50%, respectively, with no significant difference. The rate of UN-FNAC observed was 95.3% in ACR-TIRADS, 90.3% in EU-TIRADS, and 92.4% in K-TIRADS, with no significant difference. Figure 1 summarizes all study results.

Discussion

The rate of UN-FNAC is a major endpoint to investigate the performance of TIRADSs. The ideal TIRADS should indicate FNAC in cancers and avoid FNAC in benign lesions. In clinical practice, this is not possible. Thus, developing a well-balanced TIRADS with a low UN-FNAC rate and the highest possible frequency of cancer detection is a current challenge in the perspective of the ongoing important project of I-TIRADS (11). The present study aimed to analyze the setting of TNs assessed as category 3 (low risk) according to the most popular TIRADSs. Low-risk TNs represent a major burden of UN-FNAC in clinical practice, with lower likelihood of cancer than the intermediate- and high-risk categories.

About one hundred consecutive TNs with histological diagnosis were collected for each of the three TIRADSs. The results can be outlined as follows. First, the cancer frequency observed in category 3 of the three TIRADSs was higher than expected after reading the guidelines, especially ACR- and EU-TIRADS. Second, the frequency of TNs with indication for FNAC was around 50% according to ACR- and EU-TIRADS, and two-thirds according to K-TIRADS. Third, the UN-FNAC rate was important in all three TIRADSs, with the highest percentage in ACR-TIRADS. As the study findings look interesting, a clinically oriented discussion is needed. Certainly, a rule-out strategy for TNs is needed, as recommended by international societies (12, 13). The frequency of low-risk TNs within the huge number of patients with nodular goiter is important, especially when looking at

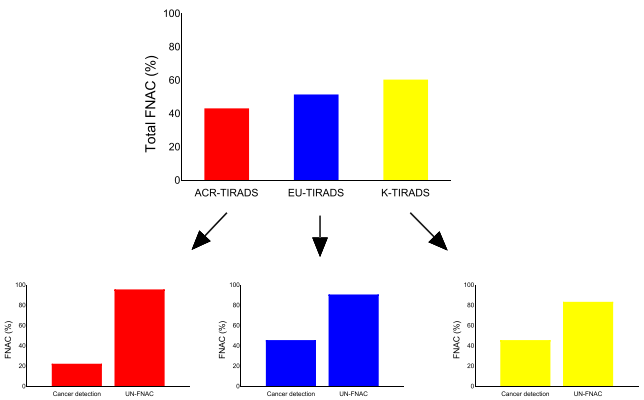

Figure 1

Summary of the study results. Numbers and frequencies are detailed in the text. UN-FNAC, unnecessary fine-needle aspiration cytology.

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cases with multiple lesions. As US is universally recognized as the main diagnostic step in the initial TN assessment, we should have an excellent performance of TIRADS as a rule-out strategy. The largest part of TNs is benign. A large percentage of them present on US as isoechoic or partially cystic and are then assessed as category 3 (low risk) by TIRADSs. All US-based risk stratification systems have been conceived on the basis of PTC US presentation, and the evidence-based studies showed that TIRADS performance was basically demonstrated only against PTC (14). However, FTC and MTC have heterogeneous US presentations and can be assessed as TIRADS 3 or 4 (15, 16). In addition, PTC rarely presents as low/intermediate-risk lesion. Finally, the most popular TIRADSs suggest various TN size thresholds to indicate or not indicate FNAC (3, 4, 5). From this point of view, the attempt of ACR-TIRADS to higher the TN FNAC cut-off to 2.5 cm with the intent to reduce UN-FNAC as much as possible appears ineffective or, at least, debatable. On one hand, the total number of FNACs indicated in low-risk TNs according to ACR-TIRADS was significantly lower than that of K-TIRADS. On the other hand, unfortunately, the rate of UN-FNAC in this low-risk setting remained very high and, even if not significantly, was higher than that of the other two systems. In addition, the cancer detection of the three systems was unsatisfactory, with worse accuracy in ACR-TIRADS. In addition, the number of TNs assessed as TIRADS 3 in a consecutive series of patients was similar across ACR-, EU-, and K-TIRADS. Finally, the cancer rate among TNs assessed as low risk was not negligible in the ACR-, EU-, and K-TIRADS series, with no significant difference.

Overall, considering that the complexity in the interpretation and application of multiple guidelines for TNs is a matter of debate (17), and taking into account that the various TN size thresholds were arbitrary proposals from expert panels and have been challenged in the literature (18, 19, 20, 21), alternative strategies to reduce UN-FNAC in the low-risk setting are warranted. As mentioned above, adopting a high TN size cut-off may not be effective in reducing UN-FNACs. Rather than indicating FNAC in low-risk TNs according to arbitrary fixed cut-offs, we should employ a patient-oriented strategy and then indicate FNAC in scenarios where clinicians are asked to act: a) TN growing and/or showing echostructure changes over time, b) patient with TN-related local symptoms needing treatment (surgery or non-surgical options), c) patient with previous – other than US – imaging procedures reporting suspicious or worrisome features (i.e. FDG avidity on PET, and suspected extra-thyroidal extension on computed tomography), d) patient followed up for non-thyroidal oncology with potential thyroid involvement, e) patient with suspicious/indeterminate levels of circulating markers (calcitonin or other). This clinically oriented strategy could be effective in patients with TIRADS 3 TNs and merits future specific prospective studies.

Even if the study protocol included only a retrospective analysis of cases undergoing surgery, with potential selection issues, a consecutive series of FNACs performed at our institution was reviewed with the purpose of calculating the rate of UN-FNAC in nodules undergoing cytological assessment. During the study period, 1,013 FNACs were performed at our institution, and 414, 462, and 473 were classified as ACR-TIRADS 3, EU-TIRADS 3, and K-TIRADS 3, respectively; among them, we could observe a rate of UN-FNAC of 78.3, 76.4, and 76.9% according to the three TIRADSs, respectively (data not shown). This finding further indicates that we need to develop further strategies to better select cases for FNAC and reduce the burden of UN-FNACs.

Limitations of the present study need to be addressed. i) This is a retrospective analysis of patients undergoing thyroid surgery according to multiple indications, with risk of selection bias. ii) The retrospective assessment of TNs was based on US frozen images available in the institutional RIS-PACS, with risk of performance bias. However, this study has strengths to emphasize. i) The herein selected histological series allowed to fully evaluation of the study endpoint in a setting including various diagnoses. As intrinsically demonstrated by the present results, the TN size threshold to indicate or not indicate FNAC in the TIRADS 3 category is quite high, with the unavoidable risk of not performing FNAC in small cancers. ii) The study design included a risk assessment of cases by one expert US operator blinded to the diagnosis. The final histological diagnosis and the TIRADS data were aligned by a second operator only in a second step. This strategy can reduce biases.

In conclusion, the issue of how to save on UN-FNAC in low-risk TNs remains debated. The cancer rate observed in a setting of TNs assessed as TIRADS is around 10% and higher than that initially estimated in TIRADS guidelines. Although a higher TN size threshold to indicate FNAC can be effective in reducing the total number of FNACs in the huge number of TIRADS 3 cases, the rate of UN-FNAC does not decrease. Alternative strategies should be investigated before the I-TIRADS is developed and published (11).

Declaration of interest

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

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Author contribution statement

AL and PT contributed to the study conception and design; material preparation, data collection, and analysis were performed as reported in the Methods section. The first draft of the manuscript was written by PT, and all authors provided comments on previous versions of the manuscript.
All authors read and approved the final manuscript.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Compliance with ethical standards

This retrospective study was approved by the Ethics Committee of Tessin Canton (Switzerland). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patient consent

Informed consent was obtained from all subjects involved in the study according to the protocol approved by the Ethics Committee of Tessin Canton (Switzerland).

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