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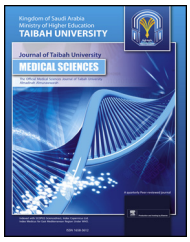

Original Article

The impact of thyroid imaging reporting and data system on the management of Bethesda III thyroid nodules☆

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الملخص

أهداف البحث: النوع ذو الأهمية غير المحددة أو الآفة الجريبية ذات الأهمية غير المحددة هي فئة غير متجانسة في علم الخلايا الشفط بالإبرة الدقيقة ، والتي لا تزال إدارتها مثيرة للجدل. تكمن الأهمية السريرية لهذه المجموعة في استبعاد الأورام الخبيثة. هدفت الدراسة الحالية إلى تحديد مدى صلاحية إرشادات نظام البيانات وتقارير التصوير الدرقي للكلية الأمريكية للأشعة (2017) في التنبؤ بالأورام الخبيثة على وجه التحديد في هذه الفئة.

طريقة البحث: استخدمت هذه الدراسة مجموعة من دراسة سابقة بأثر رجعي من قبل المؤلفين. تضمنت هذه الدراسة الأتراب بأثر رجعي التي مدتها أربع سنوات جميع الحالات التي تم تشخيص خلوي لأنماط ذات أهمية غير محددة أو آفة جرابية ذات أهمية غير محددة. ضمت الدراسة 110 حالة مع التشخيصات النسيجية المرضية النهائية الموثقة والفحوصات بالموجات فوق الصوتية.

النتائج: شملت الدراسة 83 أنثى (75.5٪) و 27 ذكر (24.5٪) مريض. كان الخطر الإجمالي للأورام الخبيثة في النوع ذي الأهمية غير المحددة أو الآفة الجريبية ذات الأهمية غير المحددة لعقيدات الغدة الدرقية 47.3 ٪. كانت نسبة الأورام الخبيثة في نظام الإبلاغ والتصوير بالغدة الدرقية بالكلية الأمريكية للأشعة 3، و 4، و 5 كالتالي: 43.5٪ ، 49.4٪ ، 40٪ على التوالي. لم تحقق العلاقة بين الإبلاغ عن تصوير الغدة الدرقية ونظام البيانات وعلم الأمراض النهائي دلالة إحصائية.

الاستنتاجات: يعد فحص الخلايا بالإبرة الدقيقة المتكرر مع وجود نوع أولي ذي أهمية غير محددة أو آفة جرابية ذات عقيدات ذات أهمية غير محددة أمرا بالغ الأهمية. أشارت النتائج التي توصلنا إليها إلى أن نظام بيانات وتقارير تصوير الغدة الدرقية بالكلية الأمريكية للأشعة لم يساهم في التقسيم الطبقي لمخاطر الإصابة بالسرطان لأنواع ذات أهمية غير محددة أو آفة جرابية من عقيدات ذات أهمية غير محددة. مطلوب دراسة مستقبلية كبيرة متعددة المؤسسات لتحديد مدى صحتها وما إذا كانت الأدوات السريرية أو الخلوية أو الجزيئية أو البيوكيميائية الأخرى المساعدة يمكن أن تساعد في إدارة هذه العقيدات غير المتجانسة.

الكلمات المفتاحية: الكلية الأمريكية للأشعة نظام الإبلاغ عن تصوير الغدة الدرقية والبيانات؛ نوع ذو أهمية غير محددة / آفة جرابية ذات أهمية غير محددة؛ بيثيسدا الثالث

Abstract

Objectives: Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) is a heterogeneous category of fine needle aspiration cytology (FNAC); the management of this condition remains controversial. The clinical significance of such patients relies on the exclusion of malignancy. In this study, we aimed to determine the validity of the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) (2017) for predicting malignancy in this specific category of patients.

Methods: In this study, we analysed a cohort of patients from our previous retrospective study. This four-year retrospective cohort study included all cases undergoing surgery with a cytological diagnosis of AUS/FLUS. We enrolled 110 cases with documented final histopathological diagnoses and ultrasound examinations.

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Results: The study included 83 females (75.5%) and 27 males (24.5%). The overall risk of malignancy (ROM) for AUS/FLUS thyroid nodules was 47.3%. The ROMs of TI-RADS 3 (TR3), TI-RADS 4 (TR4), and TI-RADS 5 (TR5) were 43.5%, 49.4% and 40%, respectively. There was no significant association between TI-RADS and final pathological analysis.

Conclusions: Repeated FNAC with initial AUS/FLUS nodules is crucial. Our findings showed that ACR TI-RADS did not contribute to the cancer risk stratification of AUS/FLUS nodules. A large prospective multi-institutional study is now required to determine the validity of ACR TI-RADS and whether other adjunct clinical, cytological, molecular, or biochemical tools could facilitate the management of patients with these heterogeneous nodules.

Keywords: American College of Radiology Thyroid Imaging Reporting and Data System; Atypia of undetermined significance/follicular lesion of undetermined significance; Bethesda III

Introduction

Thyroid nodules (TNs) are a prevalent problem that requires the exclusion of cancer. On ultrasound (US), the prevalence of TNs ranges from 20% to 76% with overall malignancy occurring in 5−15% of cases.[1,2] Certain factors, including sex, age, a history of radiation exposure, a family history of thyroid cancer, and certain ultrasonographic characteristics, increase the risk of malignancy (ROM).[3]

Fine needle aspiration cytology (FNAC) is an essential step in the evaluation of TNs. According to the Bethesda System for reporting thyroid cytopathology, TNs are classified into six categories.[4] Of categories, indeterminate nodules (atypia of undetermined significance [AUS] or follicular lesion of undetermined significance [FLUS]) and IV (follicular neoplasm [FN] or suspicious for a follicular neoplasm [SFN]) represent approximately 25% of all FNAC diagnoses.[2]

TNs with AUS/FLUS are a heterogeneous category with a ROM ranging from 5% to 15%[4]; however, there are variations among institutions with ROM ranging from 15.7% to 54.6%.[5] These nodules have been studied from different aspects, including clinical and radiological features (such as the Thyroid Imaging Reporting and Data System [TI-RADS]), cytological subtypes, molecular testing and puncture feeling techniques.[6−9] The overall goal is to establish a diagnosis in order to manage malignant nodules and avoid unnecessary surgeries for cases involving asymptomatic benign lesions.[10]

Horvath et al. first established the TI-RADS in 2009. These authors identified ten ultrasonographic criteria and linked the ROM to these criteria.[11] Soon after, Park et al. proposed another protocol in which 12 sonographic features were applied to stratify the ROM.[12] Later, various systems with modified interpretations were implemented.[13−15] The American College of Radiology TI-RADS (ACR TI-RADS) guidelines were established in 2017; this system aimed to unify reporting in the US and stratify the ROM.[16] However, none of these systems can accurately distinguish between benign and malignant TNs, thus necessitating histopathological examination for a definitive diagnosis.[3]

Because of their heterogenecity, the clinical management of AUS/FLUS is still debatable. Nonetheless, repeat FNAC, molecular testing or lobectomy are suggested.[17] Despite its utility for preoperative diagnosis, molecular testing may be impractical due to its high cost and inaccessibility in most centres.[10] In this study, we aimed to apply the ACR TI-RADS (2017) on a patient cohort that we analysed in a previous study.[6] To the best of our knowledge, this is the second study from KSA investigating the utility of ACR TI-RADS (2017) for cancer risk stratification in AUS/FLUS TNs.[18] In the current study, we extended the findings of this earlier study by investigating the relationship between additional factors and ROM, such as nodule site and biopsy method.

Materials and Methods

This retrospective study was carried out in a single center.

We used the same dataset utilized by our research group in a previous study[6] which included all primary TNs with a cytological diagnosis of AUS/FLUS that eventually underwent surgery. However, only patients with a complete

Table 1: Baseline features of Bethesda III thyroid nodules.

Variable	Distribution
Gender (n = 110)	
Male	27 (24.5%)
Female	83 (75.5%)
Age, years	41 ± 11.7
Final Pathology	
Benign	58 (52.7%)
Malignant	52 (47.3%)
Biopsy Method (n = 109)	
US-guided	71 (65.1%)
Palpation-guided (pathologist)	4 (3.7%)
OSI	34 (31.2%)
Composition	
Cystic or completely cystic	8 (7.3%)
Solid or almost completely solid	102 (92.7%)
Echogenicity	
Hypoechoic	60 (54.5%)
Hyperechoic or isoechoic	50 (45.5%)
Shape	
Wider-than-tall	110 (100%)
Margin	
Smooth	64 (58.2%)
Ill-defined	46 (41.8%)
Echogenic foci	
Macrocalcifications	23 (20.9%)
None	87 (79.1%)

OSI, outside institution; US, ultrasound.

set of final pathological diagnoses and US examinations were selected for this research.

The 2017 ACR TI-RADS score was calculated by an expert radiologist (MAA) who was blinded to the final histopathological diagnosis. The score was based on the sum of the following points: 0 points (TR1, benign), 2 points (TR2, not suspicious), 3 points (TR3, mildly suspicious), 4–6 points (TR4, moderately suspicious), and ≥7 points (TR5, highly suspicious). We also considered that point calculations can be influenced by the following factors: composition, margin, echogenicity, echogenic foci and shape.[16]

Statistical analysis

SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was utilized for data analysis. Frequencies and percentages were used to describe categorical data. Medians and interquartile ranges were used to describe quantitative variables. Univariate comparisons were performed with the Chi-squared test while Fisher's exact test or the independent t-test was used for categorical and continuous variables, respectively. A P-value < 0.05 was considered statistically significant. Risk of malignancy (ROM) was calculated by dividing the number of malignant nodules by the total number of nodules tested in each group according to the following formula: (ROM = number of malignant outcomes/populations at risk × 100).

Results

A total of 110 patients met our inclusion criteria and were included in the final analysis. Patient age ranged from 15 to 71 with a mean of 41 ± 11.7 years. The vast majority of patients (n = 83, 75.5%) were female. The final histopathology was benign in 58 patients (52.7%) and malignant in 52 patients (47.3%). Papillary thyroid carcinoma (PTC) was the most common type of malignant thyroid cancer (42%). Follicular thyroid carcinoma (FTC) and lymphoma were found in 2.7% and 1.8% of patients, respectively.

The overall ROM in our study was 47.3%. The FNAC was repeated in 45 patients (40.9%). Twenty of these (44.4%) resulted in the same cytological diagnosis of AUS/FLUS. The ROM in repeated FNAC patients was 55.6%. Notably,

Table 2: Association between different parameters and final pathology.

Variables	Number of nodules	Pathology		*ROM*	Significance *P*-value*
		Benign	Malignant		
Age	110	41 ± 11.4	40.7 ± 12.2	47.3	0.61
Gender					**0.02***
Male	27	9 (15.5%)	18 (34.6%)	66.6	
Female	83	49 (84.5%)	34 (65.4%)	40.9	
Biopsy Method	109				0.42
US-guided	71	41 (70.7%)	30 (58.8%)	42.2	
Palpation-guided	4	2 (3.4%)	2 (3.9%)	50	
OSI	34	15 (25.9%)	19 (37.3%)	55.8	
Composition					0.17
Cystic or completely cystic	8	6 (10.4%)	2 (3.8%)	25	
Solid or almost completely solid	102	52 (89.6%)	50 (96.2%)	49	
Echogenicity					0.80
Hyperechoic or isoechoic	50	27 (46.6%)	23 (44.2%)	46	
Hypoechoic	60	31 (53.4%)	29 (55.8%)	48.3	
Shape					0.98
Wider-than-tall	110	58 (100%)	52 (100%)	47.3	
Margin					0.77
Ill-defined	46	25 (43.1%)	21 (40.4%)	45.6	
Smooth	64	33 (56.9%)	31 (59.6%)	48.4	
Echogenic foci					0.59
Macrocalcifications	23	11 (19%)	12 (23.1%)	52	
None	87	47 (81%)	40 (76.9%)	46	
Site					0.79
Isthmus	3	1 (1.7%)	2 (3.8%)	66.6	
Right side	60	32 (55.2%)	28 (53.8%)	46.7	
Left side	47	25 (43.1%)	22 (42.4%)	46.8	
Size					0.42
Large (>1 cm)	96	52 (89.7%)	44 (84.6%)	45.8	
Small (<1 cm)	14	6 (10.3%)	8 (15.4%)	57.1	
TI-RADS					0.64
TR1	1	1	0	0	
TR2	0	0	0	0	
TR3	23	13	10	43.5%	
TR4	81	41	40	49.4%	
TR5	5	3	2	40%	

* Statistically significant at $P < 0.05$.

Table 3: Comparison between the ROM in AUS/FLUS nodules among different centers in KSA.

Study	Reference	Year	City	Rate of AUS/FLUS	Number of resected nodules	Overall ROM	ROM in Second FNAC
Al Dawish et al.	18	2020	Riyadh	9.6%	167	27.6%	34.4%
Alshahrani et al.	24	2021	Riyadh	–	187	46.5%	–
Alqahtani et al.	29	2022	Tabuk	6.4%	29	44.8%	–
Present Study	–	2022	Riyadh	13.7%	110	47.3%	55.6%

there was a statistically significant relationship between repeated FNAC and the final pathology ($p < 0.05$).

Table 1 shows the patient demographics and US characteristics of Bethesda III TNs. In 102 (92.7%) patients, the composition was solid or almost completely solid. Hypoechoic TNs were recorded in 60 patients (54.5%), while the remaining TNs were hyper or isoechoic. Smooth margins were found in 64 patients (58.2%) while ill-defined margins were found in only 46 patients (42%). Almost 81% of the TNs had no echogenic foci; the remaining TNs had macrocalcifications.

Table 2 shows the association between final pathology and various parameters. There was a significant relationship between sex and final pathology ($p < 0.05$). In contrast, no statistical significance was found between age, biopsy method, nodule site (right versus (vs.) left vs. isthmus), nodule size and the final pathology. Furthermore, there was no significant association between various US features or TI-RADS and the final pathology.

Discussion

The optimal management of AUS/FLUS TNs remains a significant challenge. Therefore, different tools have been developed and used to study and evaluate AUS/FLUS TNs. These include clinical aspects, radiological features (TI-RADS), cytological subtypes, molecular testing, and puncture feeling techniques.[6–9] In this study, we explored the impact of ACR TI-RADS on cancer risk stratification in patients with AUS/FLUS TNs.

In our cohort, most patients were female (n = 83; 75.5%); this finding is consistent with a previous study.[18] However, male patients had a higher ROM (66.6%, $p = 0.02$); this finding was different from other reports.[18–20]

Our data showed that the overall ROM was 47.3%; this was in accordance with previous studies.[5] The ROM for repeated FNAC was 55.6%; this also concurred with previous reports.[18,21] Table 3 shows a comparison between the ROM in AUS/FLUS nodules among different centers in KSA. Notably, there was a statistically significant association between the ROM and the repeated FNAC (p 0.007), thus indicating the importance of repeating FNAC to further classify AUS/FLUS nodules. This finding supports the previous findings of Valerio et al. and Bahaj et al.[22,23]

Our data found no significant association between the nodule site (right vs. left vs. isthmus) and the final pathology. This contradicts the findings of a retrospective study involving AUS/FULS nodules, which found a significant association between nodule site (right vs. left vs. bilateral) and the final pathology ($p < 0.001$).[24] Moreover, our findings found no correlation between nodule size and final pathology; this concurred with previous studies.[20,25]

Certain radiological features were found to lead to a general increase in the ROM of TNs. These features included rim calcifications with small extrusive soft tissue components, microcalcifications, irregular margins, solid components, a hypoechoic nature, a shape that is taller rather it is wide, and evidence of extrathyroidal extension. The probability of such a risk is known to range from 70% to 90%.[26] On the other hand, some authors believed that US features can be used to determine which AUS patients can undergo surgery.[7] Furthermore, other researchers argued that US is a valuable tool for distinguishing benign from malignant AUS/FLUS TNs.[10] Interestingly, it has been found that some US features are a valuable diagnostic tool for estimating the ROM in indeterminate TNs, particularly in light of recent changes in the cytopathologic diagnostic system.[27] In contrast, our results demonstrated that US findings had little value in distinguishing benign from malignant TNs; this was consistent with previously published reports.[25,28]

It has been reported that combining ACR TI-RADS with K-RAS mutations can facilitate risk stratification of cytologically indeterminate TNs.[2] Furthermore, some authors concluded that the ACR TI-RADS was beneficial for stratifying cancer risk in AUS/FLUS TNs.[18] Moreover, other investigators have argued that the TI-RADS showed at least some correlation between malignant or benign cytological diagnoses.[3] In contrast, other reports showed that ACR TI-RADS does not help in predicting the ROM in patients with Bethesda III nodules[28,29]; this concurs with our present findings.

The ROMs in this study were 43.5% (TR3), 49.4% (TR4), and 40% (TR5). Al Dawish et al. previously reported ROMS of 14.3% for TR2, 21.5% for TR3, 23.7% for TR4 and 55.2% for TR5.[18] On the other hand, Wu et al. reported ROMs of 0% for TR2, 40% for TR3, 6.7% for TR4 and 52.9% for TR5; notably, these authors simultaneously studied Bethesda III and IV TNs.[2] Furthermore, in a study involving indeterminate nodules, Barbosa et al. reported ROMs of 23.3% for TR3, 49.6% for TR4, and 92.9% for TR5.[10]

We believe that the current study has several strengths. First, this study is the second national study investigating the validity of ACR TIRADS (2017) in AUS/FLUS TNs. Second, unlike the previous study by Al Dawish et al.,[18] we investigated other factors (such as nodule site and biopsy method) in relation to ROM. However, our study also has some limitations that need to be considered, such as its retrospective nature, small sample size and single-institution study design. Furthermore, we only included the resected nodules; hence, selection bias was unavoidable.

Conclusions

Analysis showed that US features and the ACR TI-RADS did not contribute to cancer risk stratification in AUS/FLUS nodules. Prospective multi-institutional research is now needed to determine the validity of the ACR TI-RADS and identify other clinical, cytological, molecular or biochemical tools that could aid in the management of these heterogeneous nodules.

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Conflict of interest

The author(s) have no conflict of interest to declare.

Ethical approval

The ethical approval was obtained for this study from the Office of Research Affairs at King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia (RAC number 2225214) on 18 July 2022.

Consent

The consents of patients are not required.

Authors contributions

SMA and SSA conceived and designed the study and conducted the research. SMA organized the data. MAA and RIA contributed to the acquisition, review and interpretation of radiological images. SMA, SSA and HNH analysed and interpreted the data. SMA wrote the initial and final draft of the article and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Registration number in case of a clinical trial and where it is registered

Not applicable.

Guarantor

Saad M. Alqahtani.

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