Original Article

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Radiology Section

Diagnostic Value of Applying ACR-TIRADS on Thyroid Nodule Biopsies at a Tertiary Care Centre in the United Arab Emirates: A Prospective Observational Study

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ABSTRACT

Introduction: Incidental thyroid nodules are commonly encountered in clinical practice, and only a minority of these are malignant. Suspicious nodules on ultrasound are subjected to Fine Needle Aspiration Biopsy (FNAB) to rule out malignancy and determine appropriate management. In the United Arab Emirates, medical professionals from various countries practice, and there are no well-established local best practice guidelines for thyroid nodule biopsies.

Aim: To determine the percentage of thyroid nodules in which FNAB would be considered unnecessary by applying the American College of Radiology (ACR)-Thyroid Imaging Reporting and Data System (TIRADS) 2017 guidelines.

Materials and Methods: A prospective observational study was conducted in the Radiology Department of Belhoul Speciality Hospital, Dubai, United Arabs Emirates from January 2018 to December 2019. A total of 142 thyroid nodules were studied, and FNABs were performed. Two experienced radiologists assigned ACR-TIRADS categories to the nodules. The nodules were divided into groups: Fine-Needle Aspiration (FNA) indicated and FNA not indicated. Surgically resected nodules underwent histopathological examination, and benign or malignant categorisation was based on histopathological findings. Cases with Bethesda II cytology were considered benign, Bethesda V and VI were considered malignant, and 35 cases with Bethesda I, III, or IV cytology were excluded from the study. The final study cohort included 107 nodules with available final reference standard diagnoses. Data were analysed using International Business Machine Statistical Package for Social Sciences (IBM SPSS) Statistics 26.0, and sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Diagnostic Odds Ratio (DOR) {each with 95% Confidence Interval (CI)} were calculated.

Results: Out of the 107 nodules included in the study, 15 (14%) were malignant, and 92 (86%) were benign. Applying ACR-TIRADS, biopsy was not indicated in 54 out of 107 patients, resulting in an "unnecessary" biopsy rate of 50.5%. Only two out of the 15 malignant cases were assigned to the FNAC not indicated group due to their subcentimetre size. Therefore, the sensitivity, NPV, and false negative rate of these criteria were 86.7%, 96.3%, and 3.7%, respectively.

Conclusion: The ACR-TIRADS guidelines are highly reliable, and if strictly followed, almost half of thyroid nodule biopsies can be safely avoided. However, since ACR-TIRADS does not recommend FNA for subcentimetre thyroid nodules, a few small malignancies may experience delayed diagnosis.

Keywords: American college of radiology-thyroid imaging reporting and data system, Cytodiagnosis, Fine needle biopsy, Thyroid neoplasm, Ultrasonography

INTRODUCTION

Since up to 68% of adults show thyroid nodules on high-resolution ultrasound [1], incidental thyroid nodules are a common clinical occurrence. The majority of these incidental thyroid nodules are benign in nature, and only a minority of them have suspicious or malignant features requiring further management [2]. FNA is currently the most commonly used technique to determine the nature of the nodule and guide its management [3]. However, performing FNA on every single nodule is impractical due to their high prevalence. Therefore, it is crucial to accurately determine which nodules should be sampled and which can be safely followed-up clinically. Various national and international thyroid societies have developed ultrasound-based risk stratification systems aiming to detect the highest possible percentage of thyroid malignancies while minimising unnecessary FNAB procedures [4-12]. Several large retrospective studies and a few prospective studies [13,14] have been conducted to validate these risk stratification systems and evaluate their relative strengths and weaknesses.

Recent studies involving large databases [13-21] have concluded that, compared to other systems, the 2017 American College of Radiology-Thyroid Imaging Reporting and Data System (ACR-TIRADS) more effectively reduces unnecessary biopsies performed on benign thyroid nodules. Additionally, another recent study found that using ACR-TIRADS, all thyroid nodules could be classified, whereas a minority of nodules remained unclassified using the Korean Society of Thyroid Radiology TIRADS and American Thyroid Association (ATA) guidelines [22].

Based on the results from previous studies, authors decided to apply only the ACR-TIRADS system in the present study. In the United Arab Emirates, medical professionals from various countries practice, and there are no well-established local best practice guidelines for thyroid nodule biopsies. Therefore, authors conducted a prospective observational study to evaluate the potential impact of applying the ACR-TIRADS system on thyroid nodule sampling in the study institution. Our study aimed to determine the percentage of nodules in which FNAB would have been considered unnecessary according to ACR-TIRADS guidelines, and to calculate the accuracy of such recommendations.

MATERIALS AND METHODS

A prospective observational study was conducted in the radiology department of Belhoul Speciality Hospital from January 2018 to

December 2019. All patients (n=142) consecutively referred for thyroid nodule FNAB to the radiology department were enrolled in the study. The patients were referred by general physicians, surgeons, otorhinolaryngologists, and endocrinologists. The study received ethics approval from the Hospital's Ethics Committee (BSH/MOM/EC/17/002), and written informed consent was obtained from the patients.

Study Procedure

Pre-FNA Ultrasound examination and TIRADS scoring: Prior to each biopsy, each nodule was carefully examined using an iU 22 ultrasound system (Philips Healthcare, Bothell, Washington) with a 12 MHz linear array transducer. These images were evaluated by two radiologists experienced in thyroid imaging and were assigned a TIRADS score according to the recommendation of ACR-TIRADS [23]. The two radiologists reviewed the images together and assigned the TIRADS score by consensus.

Each nodule was given a score based on its composition, echogenicity, shape, margin, and the presence or absence of echogenic foci within the nodule [Table/Fig-1,2a-f]. Nodules with spongiform composition or mostly cystic nodules were given a score of 0. Solid nodules were assigned two points, while mixed solid-cystic nodules were given one point. Anechoic, isoechoic, hyperechoic, hypoechoic, and very hypoechoic nodules were assigned 0, 1, 2, and 3 points, respectively. Based on shape, nodules wider than tall received 0 points, whereas nodules taller than wide received 3 points. Nodules with smooth or ill-defined margins were given 0 points. Nodules with lobulated or irregular margins were assigned two points, and nodules with extrathyroid extension received three points. Nodules without any echogenic foci or with only large comet tail artifacts were given a score of 0. Nodules with macrocalcification were assigned one point, and those with rim calcification received two points. Nodules with microcalcification represented by tiny punctuate echogenic foci were given three points. The maximum size of each nodule was also recorded.

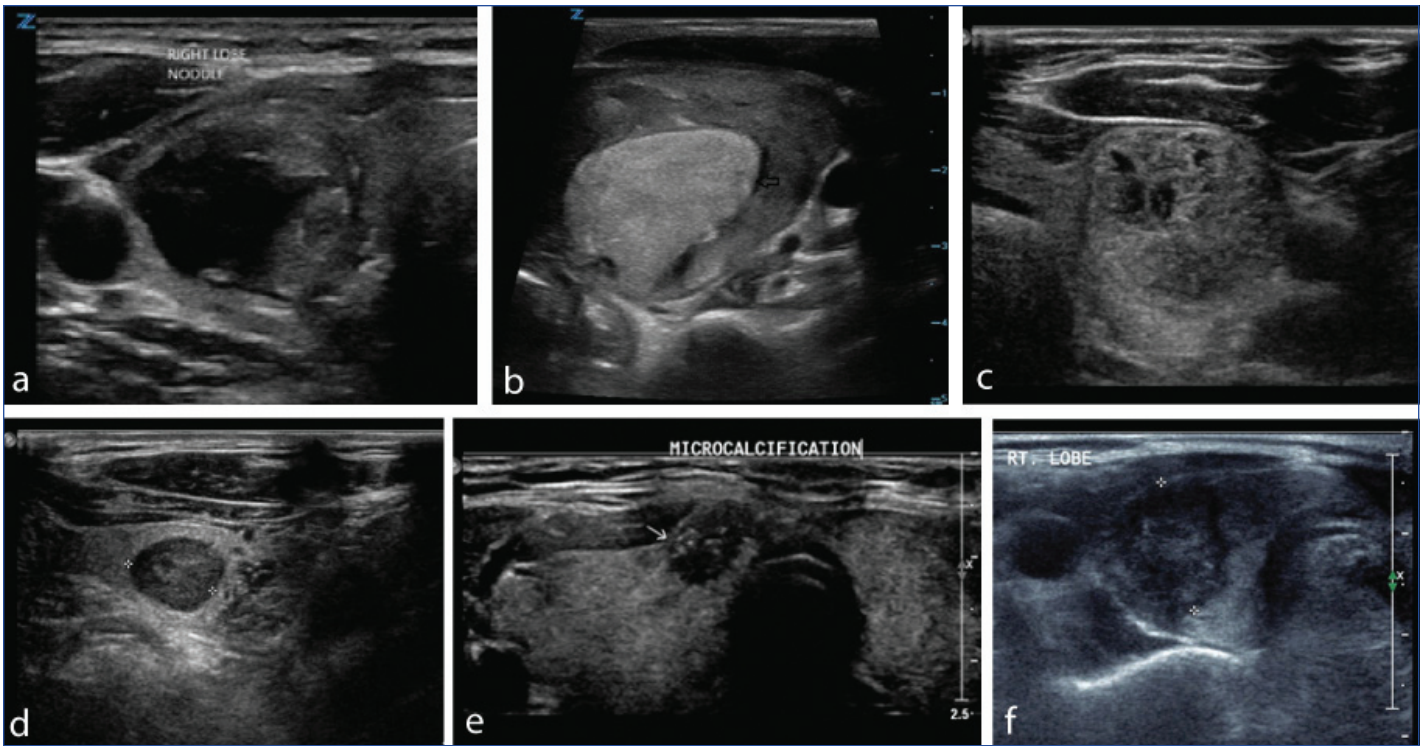
Sonographic features of nodules	Numbers (%)
Nodule composition	Spongiform or cystic-6 (5.6) Mixed cystic and solid-28 (26.2) Solid-73 (68.2)
Echogenicity	Anechoic-6 (5.6) Hyperechoic or isoechoic-59 (55.1) Hypoechoic-41 (38.3) Very hypoechoic-1 (0.9)
Shape	Wider than tall-101 (94.4) Taller than wide-6 (5.6)
Margin	Smooth or ill-defined-100 (93.5) Lobulated or irregular-6 (5.6) Extra-thyroidal extension-1 (0.9)
Echogenic foci	None or large comet tail artefacts-88 (82.2) Macrocalcifications-9 (8.4) Peripheral rim calcification-1 (0.9) Microcalcification-9 (8.4)

[Table/Fig-1]: Sonographic features of thyroid nodules.

All the scores were added, and a total score was calculated for each nodule. Nodules with a total score of 0 were grouped into the TR1 category, while those with a score of 2 were assigned to the TR2 category. Nodules with a total score of 3 were categorised as TR3. Nodules with a total score of 4 to 6 were placed in the TR4 category. Any nodule with a total score of 7 or more was classified as TR5. Therefore, all nodules were divided into these five TR categories.

Grouping of nodules on based on indication for FNA: According to ACR-TIRADS [23], TR1 and TR2 nodules are not suspicious for malignancy and thus do not require investigation with FNA. TR3 nodules are only mildly suspicious, so FNA is recommended for them only when their sizes are 2.5 cm or larger. Similarly, according to ACR-TIRADS recommendations, TR4 nodules, which are moderately suspicious, should be sampled if they have a size of 1.5 cm or larger. TR5 nodules, considered highly suspicious, should be sampled if they have a size of 1 cm or larger.

Based on these ACR-TIRADS recommendations, we categorised the nodules in our study into two groups. Group-I consisted of nodules in which FNAB was indicated, and Group-II consisted of nodules in which FNAB was not indicated [Table/Fig-3].



[Table/Fig-2]: a) Mixed solid-cystic nodule with solid component appearing iso to hyperechoic- TIRADS II nodule; cytology results: Bethesda II. b) Solid echogenic nodule with smooth margin- TIRADS III nodule; histopathology result: Follicular carcinoma. c) Predominantly solid iso to hyperechoic nodule with smooth margin- TIRADS III, cytology result: Bethesda II. d) Solid hypoechoic nodule with smooth margins- TIRADS IV; cytology result Bethesda II. e) Taller than wide solid hypoechoic nodule with microcalcification and lobulated margin- TIRADS V; histopathology- papillary carcinoma thyroid. f) Taller than wide hypoechoic solid nodule with lobulated margins- TIRADS V; histopathology: papillary CA thyroid.

TIRADS category	Number of nodules (%)	Group I (FNAB indicated)	Group II (FNAB not indicated)	Malignant	Benign
TR1	5 (4.7)	0	5	0	5
TR2	24 (22.4)	0	24	0	24
TR3	31 (29)	15	16	2	29
TR4	35 (32.7)	29	6	6	29
TR5	12 (11.2)	9	3	7	5
Total	107	53	54	15	92

[Table/Fig-3]: ACR-TIRADS classification of thyroid nodules, their grouping in FNAB indicated and FNAB not indicated groups, and malignancy distribution in these nodules.

Fine Needle Aspiration Biopsy (FNAB): All cases underwent US-guided FNAB performed by an intervention fellowship-trained radiologist (AKP). In each case, two passes were made from the nodule using a 22-gauge needle. No suction was used, and the needle was traversed several times from one margin to another margin of the nodule in multiple directions. The slides were prepared and fixed with alcohol. In cystic lesions, aspirated fluid was also stored in a sterile container and sent to the laboratory for evaluation of any malignant cells. Each specimen was analysed by experienced cytopathologists and classified according to the Bethesda classification [24].

Reference standard diagnosis: For cases that were surgically managed, the reference standard diagnosis (benign vs. malignant) was based on histopathological examination of the resected nodule. However, when the nodule was managed conservatively, the reference standard was FNA cytology. Nodules were considered benign when assigned Bethesda Class II and malignant when classified as Bethesda Class V or VI. All nodules with cytology results of Bethesda Class I, III, or IV were excluded from the study, except in cases where repeat FNACs yielded conclusive results or surgical management was performed.

STATISTICAL ANALYSIS

For the purpose of the present study, biopsies ordered in cases where they were not indicated according to the 2017 ACR-TIRADS guidelines were considered "unnecessary," and the unnecessary biopsy rate was calculated. The ACR recommendation regarding FNA was then compared with the reference standard diagnosis (benign vs. malignant) to estimate its sensitivity, specificity, PPV, NPV, and DOR, each with a 95% Confidence Interval (CI). The data were analysed using IBM SPSS Statistics 26.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

RESULTS

A total of 142 thyroid nodules were enrolled in the present study and were assessed sonographically and underwent Ultrasonography (US)-guided fine needle biopsy. Out of the 142 nodules, 35 nodules (24.6%) were excluded from the analysis because their reference standard diagnoses were inconclusive. The final study cohort included 107 nodules for which final reference standard diagnoses were available. These nodules had a size range of 6 mm to 58 mm, with a mean size of 24.72±12.14 mm. The total study population consisted of 24 males and 83 females, with a mean age of 39.35±8.28 years and an age range of 22 to 70 years. Fifteen cases (14%) met the reference standard criteria for malignancy [Table/Fig-3]. In all of these cases, the diagnosis was based on histological findings; thirteen cases were papillary thyroid cancers, including one follicular variant of papillary carcinoma, and two were follicular thyroid cancers. The remaining 92 nodules (86%) were considered benign according to the reference standard criteria. Out of these, only five cases underwent surgery, and their final diagnosis was based on benign histopathology. In the other 87 cases, the nodules yielded Bethesda Class-II cytology and were thus considered benign.

When applying the ACR-TIRADS 2017 criteria, biopsy was not indicated in 54 out of 107 patients, resulting in an "unnecessary" biopsy rate of 50.5% [Table/Fig-3]. According to these guidelines, only two out of the 15 malignant cases would have been assigned to the FNAB not indicated group (Group-II). Therefore, the sensitivity and NPV of these criteria for diagnosing malignancy in our study were 86.7% and 96.3%, respectively. The DOR was 8.45 (95% CI=1.8030% to 39.6031%, z=2.708, p=0.0068) [Table/Fig-4].

Statistic parameter	Value
Avoided biopsies	54/107 (50.5%)
False negative rate	2/54 (3.7%)
True negative rate	52/54 (96.3%)
Sensitivity (95% CI)	86.67% (59.54% to 98.34%)
Specificity (95% CI)	56.52% (45.78% to 66.83%)
Positive Predictive Value (PPV) (95%CI)	24.53% (19.31% to 30.62%)
Negative Predictive Value (NPV) (95%CI)	96.30% (87.60% to 98.97%)
Diagnostic accuracy (95%CI)	60.75% (50.84% to 70.05%)
Diagnostic Odds Ratio (DOR) (95%CI)	8.45 (1.8030% -39.6031%)

[Table/Fig-4]: Impact of ACR-TIRADS to avoid unnecessary thyroid nodule biopsies and its ability to discriminate benign from malignant nodules.

The two missed cancers in this system were subcentimetre TR5 nodules. Since FNAC is not indicated in nodules less than a centimetre in size, regardless of their sonographic features, these nodules were placed in Group-II.

DISCUSSION

If it is possible to accurately differentiate "benign" nodules from "suspicious" nodules based on their ultrasound morphological features, it would help authors avoid many unnecessary FNABs on benign nodules without the risk of missing any malignancies. In the present single-centre prospective observational study, authors found that 50.5% of thyroid nodule biopsies could have been avoided by using ACR-TIRADS sonographic risk assessment criteria. This unnecessary biopsy rate of 50.5% calculated in the present study is comparable to the rates calculated in previous, much larger studies. For example, the percentage of thyroid nodules in which ACR-TIRADS guidelines would have avoided FNAB was 53.4% and 57.8% in studies conducted by Grani G et al., and Ha EJ et al., respectively [13,21]. This inference has the potential to significantly impact the clinical management of thyroid nodules, as unnecessary FNABs cause a substantial burden on the healthcare system and considerable anxiety for patients. By strictly and universally applying these guidelines for sonographic risk assessment of nodules, almost half of the nodules referred for biopsy can be managed conservatively, thus significantly reducing biopsy-related costs and patient discomfort.

In the present cohort, the ACR criteria were found to have high sensitivity (86.7%) and high NPV (96.3%), with a false negative rate of only 3.7%. This is comparable to a previous study by Grani G et al., on unselected nodules, in which researchers found a sensitivity of 83.3%, NPV of 97.8%, and false negative rate of 2.2% [13]. A recently published meta-analysis of 16 studies calculated the pooled sensitivity and specificity of ACR-TIRADS to be 89% and 70%, respectively, which is comparable to our results [25]. In the present study, only two subcentimetre malignant nodules

were assigned to the FNAC deferrable group as per ACR-TIRADS guidelines. The disadvantage of this would have been that the diagnosis of these two cases of subcentimetre papillary carcinoma would have been delayed until they reached a size larger than 1 cm. However, since the cumulative risk of distant metastasis and cancer-specific mortality from such subcentimetre papillary cancers is very low [26], such a delay would not affect the overall prognosis. Similar to ACR-TIRADS recommendations, the ATA [27] and the Korean Society of Thyroid Radiology also do not recommend routine biopsy of nodules smaller than 1 cm, even if they are highly suspicious [28]. Subcentimetre thyroid nodules with highly suspicious ultrasonographic characteristics should be managed with active surveillance. A risk-stratified approach for active surveillance of such nodules has been suggested by Brito JP et al., which is based on the ultrasound features of the nodule, patient characteristics, as well as the expertise and experience of the medical team [29].

The specificity and PPV of the ACR guidelines in the present study were only 56.5% and 24.5%, respectively. Since these guidelines are essentially rule-out tests that primarily aim to avoid biopsies of many sonographically benign-appearing nodules, such low specificity and PPV are not surprising.

Limitation(s)

The present study included a small number of cases from a single centre. The cohort of thyroid nodules included in this study was identified for FNA by other physicians, and the criteria supporting these requests were not known. Another limitation of the present study was that the reference standard used was not error-free. For example, a benign (Bethesda Class II) cytology report was considered sufficient to classify the nodule as benign. However, the false negative rate in these cytologies is very low, estimated to be 3.7% in a recent meta-analysis [30] and even lower (<1%) in prospective series of cytologically benign nodules with no high suspicion ultrasound features [31]. Additionally, authors excluded 35 nodules with non diagnostic or indeterminate cytology, which may have introduced a selection bias. However, the proportion of nodules with such cytological reports is consistent with those reported in other cytological studies [31].

CONCLUSION(S)

In conclusion, if thyroid nodules are carefully selected for FNA based on their size and sonographic morphology, following the ACR-TIRADS recommendations, almost half of the thyroid nodule biopsies requested by physicians can be safely avoided. This may have a significant impact on clinical practice in the United Arab Emirates and other countries where there are no well-established local practice guidelines for thyroid nodule biopsies. In the present study cohort, ACR-TIRADS had a sensitivity of 86.7% for detecting malignant nodules, with an NPV of 96.3% and a false negative rate of 3.7%. The only caveat is that due to the application of a size threshold for selecting nodules for FNA, a few small malignancies may have a delayed diagnosis.

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