

Features and diagnostic accuracy of fine needle aspiration cytology of thyroid nodules: retrospective study from Oman

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Citation: Alhassan R, Al Busaidi N, Al Rawahi AH, Al Musalhi H, Al Muqbal A, Shanmugam P, et al. Features and diagnostic accuracy of fine needle aspiration cytology of thyroid: from a tertiary care center in Oman. *Ann Saudi Med* 2022; 42(4): 246-251. DOI: 10.5144/0256-4947.2022.246

Received: September 12, 2021

Accepted: January 27, 2022

Published: August 4, 2022

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Funding: None.

BACKGROUND: Fine needle aspiration cytology (FNAC) of the thyroid has been a reliable and cost-effective method for diagnosing thyroid disorders. Since FNAC results are usually operator dependent, there is a compelling need to explore FNAC accuracy among Omanis.

OBJECTIVE: Describe cytological features of FNAC and assess FNAC accuracy compared to the postsurgical histopathology report.

DESIGN: Retrospective diagnostic accuracy study

SETTINGS: Tertiary care center.

PATIENTS AND METHODS: Our study included adult Omani adult patients with thyroid nodules who underwent FNAC from 2014 to 2017 and had final pathology results for patients who underwent thyroid surgery. The results were classified according to the UK Royal college of Pathologists 'Thy' categories. Accuracy of FNAC was calculated by determining false and true positive and negative results based on histopathology findings.

MAIN OUTCOME MEASURES: FNAC accuracy (sensitivity and specificity) compared to the postsurgical histopathology.

SAMPLE SIZE: 867 patients with 1359 ultrasound guided FNACs of thyroid nodule; 137 underwent surgery.

RESULTS: The mean age of the 867 patients was 43.7 (13.3) years, with a median of 42 years, and 87.8% were females. Out of 1359 FNACs, 1001 (73.7%) were benign (Thy2), 119 (8.8%) were atypia of undetermined significance or follicular lesion of undetermined significance (Thy3a), 31 (2.3%) were follicular neoplasm or suspicious for a follicular neoplasm (Thy3f), 52 (3.8%) were suspicious for malignancy (Thy4), 55 (4%) were malignant (Thy5), 101 (7.4%) as Unsatisfactory (Thy1). Only 137 patients underwent thyroid surgery, and the FNAC reports were compared with their final histopathology reports. The sensitivity, specificity and total accuracy of FNAC were 80.2%, 98.9% and 89.9%, respectively. The positive and negative predictive values of FNAC were 98.6% and 84.3%, respectively.

CONCLUSION: Our study findings confirmed that FNAC of the thyroid is a sensitive, specific, and accurate initial tool for the diagnosis of thyroid lesions. Most of the FNACs were benign with a very low malignancy rate. Due to the minimal chance of false negative results and the slow-growing nature of thyroid malignancy, it is important that patients with benign FNAC should have periodic clinical and radiological follow-up.

LIMITATIONS: Retrospective design and single-center study, and thyroid nodule size unavailable.

CONFLICT OF INTEREST: None.

Thyroid nodules are widespread; 4-7% of adults have palpable nodules. Due to the widespread use of ultrasound (US) as a screening tool, many people are incidentally noted to have impalpable nodules.^{1,2} More than 95% of these thyroid nodules are benign.³ To avoid unwanted invasive thyroid surgeries, it is always better to operate on patients when there is a high suspicion of malignancy. However, clinical presentation alone cannot distinguish benign and malignant lesions.⁴

Thyroid fine-needle aspiration cytology (FNAC) was first described in 1948.⁵ FNAC had emerged as a trustworthy, cost-effective, and time-saving tool to diagnose and manage significant thyroid nodules and reduce the rate of unnecessary thyroid surgery, mainly when ultrasound guidance FNA was performed.⁶ The UK Royal College of Pathologists (RCPATH) 'Thy' categories for reporting thyroid cytopathology are widely used to guide discussion on further management of thyroid nodules using the Thy classification.^{7,8} Numerous studies have been published describing FNAC results of thyroid nodules and their accuracy in different parts of the world. Overall, FNAC is reported as being an accurate tool for diagnosing thyroid lesions. A study from France that included 166 patients showed that the diagnostic accuracy was about 89%, with a sensitivity of 68% and specificity of 99.2%.⁹ Another study from Egypt showed a sensitivity of 92.8% and specificity of 94.2%, with a total accuracy of 93.6%.¹⁰

According to the Oman National Cancer Registry (ONCR) Thyroid Cancer, the overall age standardized rate (ASR) from 1996 to 2015 was 5.5 /100 000 (7.6 for females and 2.0/100 000 for males),¹¹ While the thyroid cancer ASR was 4.4/100 000 for Saudi Arabia and 5.1/100 000 for the UAE.^{12,13} Local studies related to thyroid FNAC accuracy are minimal and show conflicting results. One small study conducted in a tertiary care center showed that although FNAC is a sensitive method for diagnosing thyroid lesions, many patients (37.3%) showed inconclusive (unsatisfactory) test results.¹⁴ Another local study also showed low FNAC accuracy; however, this study included patients with multinodular goiter only.¹⁵ FNAC is usually operator-dependent, and hence, its accuracy may differ in different settings. Therefore, there is a compelling need to explore FNAC accuracy among Omanis. This study aims to evaluate the FNAC accuracy compared to the final histopathology report for Omani adult patients diagnosed with thyroid nodules attending a tertiary care center in Oman. We also describe the cytological features of FNAC outcomes.

PATIENTS AND METHODS

This retrospective study conducted between January 2014 and January 2017 at a tertiary endocrine center in Oman included all patients with single or multiple thyroid nodules diagnosed by physical examination and/or by ultrasound. Demographic data such as age, gender, and the FNAC cytological report were retrieved from the electronic health record. The postsurgical histopathology report of patients who underwent surgery was also retrieved. All FNAC data were used to describe FNAC outcomes; however, only the reports of patients who underwent both FNAC and surgery were used to assess the accuracy.

All FNACs were performed under ultrasound guidance using standard procedures.¹⁶ For every nodule, the physician uses three to five separate needles, and the smears were fixed with ether/95% alcohol solution and stained by Papanicolaou's staining. Two expert histopathologists examined each smear. In case of disagreement, a third senior histopathologist was involved to reach a consensus. We classified FNAC results according to the UK Royal College of Pathologists Thy categories system for reporting thyroid cytopathology into six groups; non-diagnostic or unsatisfactory (Thy1), benign (Thy2), atypia of undetermined significance or follicular lesion of undetermined significance (Thy3a), follicular neoplasm or suspicious for a follicular neoplasm (Thy3f), suspicious for malignancy (Thy4), and malignant (Thy5). We considered Thy2 as a benign result and Thy4 and Thy5 as a positive test for malignancy, Thy1 as non-diagnostic, and Thy3a and Thy3f as an intermediate result (**Table 1**).

The FNAC results were compared with the post-surgery histopathology. Sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), and negative predictive value (NPV) of FNAC were calculated. Since it was challenging to include non-diagnostic (Thy1) cases and an intermediate category (Thy3a and Thy3f) under benign or malignant categories, those were excluded from the analysis. IBM SPSS version 23 program (Armonk, New York, United States: IBM Corp) was used for statistical analysis.

RESULTS

During the study period, 867 patients underwent a total of 1359 FNACs, and all the FNACs results were included in the study. Females constituted 87.8%, and the remaining 12.2% were males. The study population's mean (SD) age was 43.7 (13.3) years, with a median of 42 years, and the minimum age being 18 years and the maximum age was 86 years. Out of the total number of FNACs, 1001 (73.7%) were reported as benign (Thy2),

52 (3.8%) as suspicious for malignancy (Thy4), 55 (4%) as malignant (Thy5), 119 (8.8%) as atypia of undetermined significance or follicular lesion of undetermined significance (Thy3a), 31 (2.3%) as follicular neoplasm or suspicious for a follicular neoplasm (Thy3f), 101 (7.4%) as non-diagnostic or unsatisfactory (Thy1).

Out of the total study population (867 patients), 137 patients underwent a thyroid surgery, and their 242 FNAC reports were compared to their postsurgical histopathology report. One-hundred eight patients with nodules in the benign category in FNAC (Thy2) went through surgery due to the large size (>4cm) of the thyroid nodule, of which 91 (84.3%) cases were confirmed benign by histopathologic examination, and the remaining 17 patients were diagnosed as malignant (Table 2). Hence, we had 91 true-negative and 17 false-negative results in the benign category, and the risk of cancer in this group was about 15.7%. Thirty-six patients with an FNA result of Thy3a underwent surgery, out of which 16 cases were malignant. The risk of cancer in this group was 33%. Fifteen cases of Thy3f underwent surgery, of which 3 cases were confirmed to be malignant, with a risk of cancer in this category was about 40%. In the FNAC malignant category (Thy4 and Thy5), 35 cases out of 52 were suspicious of malignancy (Thy4) category and 34 cases out of 55 of the malignant category (Thy5) were operated. The remaining patients either refused surgery or were treated elsewhere. In 34 cases suspicious for malignancy (Thy4), malignancy was confirmed and 1 case was reported as benign in the histopathology results. Hence, the risk of cancer in this category was 91%; however in the malignant (Thy5) category, all cases are confirmed as malignant, and so the risk of cancer was 100%. Out of the total 242 FNACs, only 178 were included for the diagnostic accuracy assessment, excluding patients with undetermined results (Table 3). Thus, FNAC achieved a sensitivity of 80.2%

(95% CI 69% - 87%), specificity of 98.9% (95% CI 93% - 99%), and a total accuracy of 89.8% (Table 4).

DISCUSSION

In this study, the RCPATH categorization system was used to study the thyroid FNAC outcomes and its accuracy among Omanis. The results of our study showed that thyroid nodules are more common among females. The study results confirmed that FNAC is a useful diagnostic tool in thyroid nodules work-up with good sensitivity and specificity. Our study showed that almost three-quarters of thyroid nodules are benign, 9% of nodules were Thy3a, 2% were Thy3f, 4% were suspicious for malignancy (Thy4), and 4% were positive for malignancy (Thy5). Our study population's rate of unsatisfactory specimens (Thy1) was relatively low, and the false-negative rate was 19.7%. These results are comparable with other studies.¹⁷⁻¹⁹

We noticed that the risk of malignancy of category Thy3a is higher than category Thy3f compared to previous studies. This could be because FNAC is usually unable to distinguish benign lesions like follicular adenomas and hyperplastic follicular nodules from malignant well-differentiated follicular carcinoma.^{1,18} The introduction of molecular tests in particular analysis for *RAS* and *BRAF* gene mutations and RT-PCR for *RET/PTC* gene rearrangements could differentiate benign from malignant lesions especially in patients who have suspicious features on US as shown in some recent studies.^{20,21}

The UK Royal College of Pathologists Thy categories for reporting thyroid cytopathology (RCPATH) was published in 2009 and reiterated in 2014.^{22,23} The system currently is of widespread use in the UK and applies to the Thy classification Thy1–Thy5.²³ Over the last decades, many other classification schemes for thyroid cytology have been introduced to guide patient management. Examples are the Bethesda system for reporting

Table 1. The UK Royal College of Pathologists 'Thy' categories for reporting thyroid cytopathology.

	Description	Plan of management
Thy1	Non-diagnostic	Repeat FNA or correlate with ultrasound if cystic nodule
Thy2	Benign	Clinical follow up with ultrasound
Thy3a	Atypia of undetermined significance or follicular lesion of undetermined significance	Repeat FNA after 3 months
Thy3f	Follicular neoplasm or suspicious for follicular neoplasm	Surgical consultation
Thy4	Suspicious of malignancy	Surgical consultation
Thy5	Diagnostic of malignancy	Surgical consultation

thyroid cytology (TBSRTC) and the Italian reporting system for thyroid cytology (TIR1-TIR5).^{24,25} These classification systems are similar but use different terminology.⁸ All include benign, malignant, suspicious for malignancy, indeterminate, and nondiagnostic categories. However, there are a few differences in the criteria used for classifying FNAC as indeterminate in each classification system. The RCPATH Thy3a category is similar to Category III (atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) of the Bethesda system. Thy3a differs partially from TIR 3A, which includes only architectural changes without atypias. In contrast, predominantly oncocyctic aspirates would be categorized as Thy3f in the RCPATH, and as TIR 3B in the Italian system. In addition, Thy2c and Thy1c of the RCPATH terminology do not clearly appear in the Bethesda system.

Although the FNAC is undoubtedly a useful diagnostic tool, it does have its limitations mainly due to sampling errors, large nodules, or misinterpretation of the cytological smear that lead to an increase in the false-negative rate (FNR) (patients with benign FNAC but histopathology after surgery shows a malignant lesion). FNRs are a serious concern as there is a possibility of missing malignant lesions, which would go untreated.²⁶ Yet, it is difficult to determine the actual FNR due to only a low proportion (about 10-15%) of patients with benign cytology undergoing surgery.²⁷ The FNR in our study was approximately 15.7%, which is well within the described numbers in the literature, which ranged between 1% and 50%.²⁸⁻³⁰ Others report FNR from 1.5% to 11.5% (average, <5%).³⁰⁻³² This variation in FNR is influenced by the number of patients who subsequently have surgery and a histologic review. In most retrospective studies, less than 10% of patients with a benign FNAC subsequently proceeded for thyroid surgery.^{31,32} Nodules with benign FNA need periodic follow-up with clinical examination and ultrasound to avoid missing malignant lesions in these nodules.^{29,30}

The rate of unsatisfactory FNACs in our study was 7.4%, and the rate reported in the literature ranges between 2% and 20%.^{18,33} Unsatisfactory FNA sampling could have occurred due to technical issues or may also result from aspiration of calcified nodules, sclerotic areas, cystic nodules, or solid nodules with cystic degeneration. The availability of technically sound expert physicians in FNAC and experienced cytopathologists is crucial to getting an optimal outcome. A repeated FNAC is recommended for unsatisfactory categories and clinically or sonographically worrisome thyroid nodules; repeat FNAC is diagnostic in 50% to 88% of cases.^{16,34-36}

Our study findings indicate that the sensitivity of FNAC is 80%, and specificity is 98% among the Omani population. These results are comparable with other studies, which have reported a range of sensitivity from 65% to 99% and specificity from 72% to 100%.³⁷⁻⁴¹ This wide range of sensitivity and specificity is due to how the authors define the false-positive and false-negative results and categorize suspicious malignant lesions. Some studies include Thy3a and Thy3f in the malignant category, while others categorize them in the negative group, whereas a few studies excluded them

Table 2. Detailed fine needle aspiration cytology and histopathological results of patients who underwent surgery (n=137 patients with 242 results).

FNAC thy code	Histopathology result		Total number
	Benign n (%)	Malignant n (%)	
Thy1	12 (85.7)	2 (14.3)	14
Thy2	91 (84.3)	17 (15.7)	108
Thy3a	16 (44.4)	20 (55.6)	36
Thy3f	12 (80.0)	3 (20)	15
Thy4	1 (2.9)	34 (97.1)	35
Thy5	0 (0.0)	34 (100)	34
Total	132 (54.5)	110 (45.5)	242

Table 3. Final FNAC versus histopathology results.

		Histopathology		Total
		Benign	Malignant	
FNAC	Benign	91	17	108
	Malignant	1	69	70
Total		92	86	178

Table 4. Accuracy measures of FNAC compared to histopathology reports (n=178).

	Percentage	95% CI
Sensitivity	80.2	70.3 - 88.0
Specificity	98.9	94.1 - 99.9
Positive predictive value	98.6	90.7 - 99.8
Negative predictive value	84.3	77.8 - 89.1
Positive likelihood ratio	73.8	10.5 - 590.9
Negative likelihood ratio	0.2	0.1 - 0.3
Total accuracy	89.9	84.5 - 93.9

Table 5. Comparison of the UK Royal College of Pathologists 'Thy' categories for reporting thyroid cytopathology (RCPATH) with other internationally used systems.

RCPATH	Bethesda	Italian
Thy1. Non-diagnostic for cytological diagnosis	I. Non-diagnostic or unsatisfactory	TIR 1. Non-diagnostic
Thy1c. Non-diagnostic for cytological diagnosis–cystic lesion		TIR 1c. Non-diagnostic–cystic
Thy2. Non-neoplastic	II. Benign	TIR 2. Non-malignant
Thy2c. Non-neoplastic–cystic lesion		
Thy3a. Neoplasm possible–atypia/non-diagnostic	III. AUS/FLUS	TIR 3A. LRIL
Thy3f. Neoplasm possible, suggesting follicular neoplasm		TIR 3B. HRIL
Thy4. Suspicious for malignancy	V. Suspicious for malignancy	TIR 4. Suspicious for malignancy
Thy5. Malignant	VI. Malignant	TIR 5. Malignant

AUS, atypia of undetermined significance; FLUS, follicular lesion of undetermined significance; HRIL, high-risk indeterminate lesion; LRIL, low-risk indeterminate lesion; RCPATH, Royal College of Pathologists.

from the calculations.³⁷⁻⁴¹ The main limitations of the study were the retrospective design and involvement of only a single center as well as the lack of thyroid nodule sizes.

In conclusion, our study findings confirmed that FNAC of the thyroid is a sensitive, specific, and ac-

curate initial tool for the diagnosis of thyroid lesions. Most of the FNACs were benign with a low malignancy rate. Due to the minimal chance of FNR and the slow-growing nature of thyroid malignancy, it is important that patients with benign FNAC should have periodic clinical and radiological follow up.

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