

# Evaluation of the Accuracy of Fine-Needle Aspiration Cytology in the Diagnosis of Thyroid Nodules: A Retrospective Analysis of Data From a Tertiary Care Hospital in Saudi Arabia

*Tiroid Nodüllerinin Tanısında İnce İğne Aspirasyon Sitolojisinin Doğruluğunun Değerlendirilmesi: Suudi Arabistan'da Üçüncü Basamak Bir Hastanenin Verilerinin Retrospektif Analizi*

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## Abstract

**Purpose:** Accurate fine-needle aspiration cytology (FNAC) of thyroid nodules provides the best guidance for thyroid surgery. We assessed the utility of FNAC in the diagnosis of thyroid nodules. Retrospective analysis.

**Material and Method:** We analyzed records of all patients who underwent FNAC and thyroid surgeries between July 2006 and June 2010 at King Khalid Hospital, King Saud University, Riyadh, Saudi Arabia. Each diagnosis derived from FNAC of thyroid nodule reported by the Bethesda system was matched with the final histopathology result. Specificity, sensitivity, positive and negative predictive value, and diagnostic accuracy were assessed.

**Results:** Of 275 FNAC, 179 (65.1%) had benign results, 60 (21.8%) atypia of undetermined significance or follicular lesion of undetermined significance, 15 (5.4%) follicular neoplasm or suspicion of follicular neoplasm, 15 (5.4%) were consistent with papillary thyroid carcinoma (PTC), and 6 (2.2%) were suspicious for PTC. Histopathology revealed 204 (74.2%) benign thyroid nodules, 44 (16.0%) PTCs, 18 (6.5%) incidental micro-PTCs in non-target nodules, 7 (2.5%) follicular thyroid carcinomas, 1 (0.4%) medullary thyroid carcinoma, and 1 (0.4%) Hürthle cell carcinoma. Analysis of 190 cases with FNAC and histopathology results revealed a sensitivity of 66.7%, specificity of 99.4%, positive predictive value of 95.2%, negative predictive value of 94.1%, and diagnostic accuracy of 94.2%. Of 10 cases with false negative results, 9 (90%) were larger than 3.8 cm.

**Discussion:** FNAC is a highly sensitive and specific method for assessing thyroid nodules. We found a high percentage of atypia or follicular lesions of undetermined significance; this needs to be limited to increase accuracy. We suggest surgery for nodules larger than 3.8 cm regardless of FNAC results due to the high false-negative rate, most likely due to sampling errors. *Turk Jem 2012; 16: 30-3*

**Key words:** Fine-needle aspiration cytology, accuracy, thyroid nodules, thyroid cancer, papillary thyroid cancer

## Özet

**Amaç:** Tiroid nodüllerinin ince iğne aspirasyon sitolojisi (TİİAS) ile doğru olarak değerlendirilmesi, tiroid cerrahisi öncesi en iyi yol göstericidir. Bu çalışmada, tiroid nodüllerinin tanısında ince iğne aspirasyon sitolojisinin yararlılığı değerlendirildi. Retrospektif analiz

**Gereç ve Yöntem:** Temmuz 2006-Haziran 2010 arasında Riyad, Suudi Arabistan'da King Saud Üniversitesi King Khalid Hastanesinde TİİAS ve tiroid cerrahisi uygulanan tüm hastaların kayıtları incelendi. Her bir tiroid nodülünün TİİAS'inin Bethesda Sistemi ile rapor edilen tanısı, nihai histopatolojik sonuç ile karşılaştırıldı. Özgüllük, duyarlılık, pozitif ve negatif prediktif değer ve tanısal doğruluk değerlendirildi.

**Bulgular:** İkiyüzetmişbeş İİAS'sinin 179'u (%65,1) benign, 60'ı (%21,8) önemi belirlenemeyen atipi ya da önemi belirlenemeyen foliküler lezyon, 15'i (%5,4) foliküler neoplazi ya da şüpheli foliküler neoplazi, 15'i (%5,4) papiller tiroid karsinomu (PTK), 6'sı (%2,2) ise şüpheli PTK şeklindeydi. Histopatolojide 204 (%74,2) benign tiroid nodülü, 44 (%16) PTK, 18 (%6,5) hedef dışı nodüllerde insidental mikro-PTK, 7 (%2) foliküler tiroid karsinomu, 1 (%0,4) medüller tiroid karsinomu ve 1 (%0,4) hürtle hücreli karsinom belirlendi. Tiroid İİAS ve histopatolojisi olan 190 vakanın analizinde, %66,7 duyarlılık, %99,4 özgüllük, %95,2 pozitif prediktif değer, %94,1 negatif prediktif değer ve %94,2 tanısal doğruluk saptandı. Yanlış negatif sonucu olan 10 vakadan 9'unda (%90) nodüller 3,8 cm'den daha büyüktü.

**Tartışma:** Tiroid İİAS, tiroid nodüllerinin değerlendirilmesinde kullanılan sensitif ve spesifik bir yöntemdir. Önemi belirlenemeyen atipi ve foliküler lezyon yüzdesinin yüksek olduğu görüldü; tanısal doğruluğun arttırılabilmesi için bu tanının sınırlandırılması gerekmektedir. 3,8 cm'den büyük nodüllerde, örnekleme hataları ile ilişkili olarak yüksek yanlış negatif oran taşınması sebebiyle, İİAS sonucuna bakılmaksızın cerrahi öneriyoruz. *Türk Jem 2012; 16: 30-3*

**Anahtar kelimeler:** İnce iğne aspirasyon sitolojisi, tiroid nodülleri, tiroid kanseri, papiller tiroid kanseri

## Introduction

Thyroid nodule is a common medical problem with a prevalence of 1% to 5% by palpation and from 19% to 67% by high-resolution ultrasound (1-3). Deciding on whether to send a patient with a thyroid nodule to surgery or not depends mainly on fine-needle aspiration (FNA) biopsy results. A comparison of FNA cytology (FNAC) results against the gold standard, the histopathological diagnosis provides a measure of FNAC usefulness. Accurate FNAC assessment of thyroid nodules would prevent unnecessary surgery with its possible complications, including injury to the recurrent laryngeal nerve, hypoparathyroidism, and thyroid hormone dependence.

Due to the simplicity, accuracy, low cost, and absence of major complications of FNA biopsy, it is considered the most reliable method for the management of thyroid nodules and should be used as the main diagnostic test (4,5). Retrospective studies have reported lower rates of both non-diagnostic and false-negative cytology specimens from FNA procedures performed under ultrasound guidance compared with palpation (6-8). The American Thyroid Association recommends FNAC as the main diagnostic test for thyroid nodules because of its superior diagnostic reliability and cost effectiveness (3). Diagnostic accuracy of FNAC varies between different series and depends in a part on the method of data analysis. Sensitivity ranges between 55% and 83%, and specificity between 74% and 98% (5,9-12). Skilled FNA technique and the availability of experienced cytologists are vital to achieving high diagnostic accuracy (8). Several diagnostic pitfalls have been described in the literature, including inadequate sampling, insufficient cellular material from cystic or hemorrhagic lesions, and limited experience of those who perform and interpret FNAC. Additionally, number of punctures and the smear preparation techniques also affect results (4,8).

Recently, The Bethesda classification system of FNAC results has been recommended to be uniformly used for reporting of FNAC (13). Limited number of studies has assessed the diagnostic usefulness of this system. Most of these studies came from the Western world. In this study, our objectives are not only to evaluate the overall accuracy of FNAC but also to evaluate this system in our practice.

## Method

A retrospective, medical chart review of patients who underwent thyroidectomy or hemithyroidectomy between July 2006 and June 2010 was conducted at King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia. Data included patient characteristics, including age, sex, and size of the nodule by ultrasound, as well as histopathology, FNAC, and postoperative histopathological results.

Criteria for inclusion were availability of records of patients who underwent thyroidectomy or hemithyroidectomy between July 2006 and June 2010, had nodules larger than 1.5 cm along at least one axis (longitudinal, anterior-posterior, transverse), and had FNAC and histopathology reports approved by a qualified consultant cytopathologist. We excluded all cases with any of the following: nodule

less than 1.5 cm on ultrasound, incomplete FNAC or histopathology report, or FNAC with no diagnostic or unsatisfactory findings.

Thyroid nodule FNA biopsy was done in the pathology department if the thyroid nodule was easily palpable. Ultrasound-guided FNA biopsy was done in the radiology department when the nodules were not palpable or were difficult to discriminate from normal thyroid tissue. 23 and 25 gauge needles were used, with 3 to 4 passes per nodule. Papanicolaou and Diff-Quik staining methods were used for slide preparation by a cytopathology technician before sending samples to the pathologist.

The reasons for hemi or total thyroidectomy were: non benign cytology results, compression symptoms, large nodules and patient preference. FNAC results were categorized according the Bethesda system 13-15 as follows:

- Nondiagnostic or unsatisfactory, including limited cellularity, no follicular cells present, poor fixation, excessive blood, and/or poor cell preservation.
- Benign, which included nodular goiter, chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), hyperplastic/adenomatoid nodule, and colloid nodule.
- Atypia of undetermined significance or follicular lesion of undetermined significance where the cytologic findings were not convincingly benign, yet the degree of cellular or architectural atypia was insufficient for an interpretation of follicular neoplasm, Hürthle cell neoplasm, or suspicious for malignancy.
- Follicular neoplasm or suspicious for follicular neoplasm, including nonpapillary follicular-patterned lesions/neoplasms and Hürthle cell lesions/neoplasms.
- Suspicious for malignancy including suspicious for papillary thyroid carcinoma (PTC), suspicious for medullary thyroid carcinoma (MTC), or suspicious for other primary or secondary malignancy.
- Malignant including PTC, follicular thyroid carcinoma (FTC), MTC, Hürthle cell carcinoma (HCC), anaplastic carcinoma, or metastatic carcinoma.

FNAC results that were nondiagnostic or unsatisfactory and continued to be the same after repeating FNA were excluded from the analysis. When we measured the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPP), and accuracy of FNAC, we labeled benign FNAC results as negative. PTC or suspicion of PTC was labeled as positive since both are indications for surgery. The histopathology report was considered negative if the result was benign and positive if the result was PTC. All FNAC false negative and false positive results were re-evaluated and confirmed. FNAC results of atypia of undetermined significance or follicular lesion of undetermined significance, and follicular neoplasm or suspicious for follicular neoplasm were evaluated separately. Histopathology report of MTC and HCC were excluded due to a small number of cases (n=2). FTC is a diagnosis that can only be made by histopathological examination, and it is almost impossible to do by FNAC; for that reason, FTC cases were not included in the analysis. Incidental findings of micro-PTC (defined as lesions <1 cm) outside the targeted nodule were not included as a positive result because micro-PTC is difficult to diagnose by FNA due to its small size and overall benign course (3).

## Statistics

Each FNAC diagnosis was matched to the histopathological result and labeled as follows: (1) true positive-positive result in the FNAC (i.e., PTC or suspicion of PTC) confirmed in the histological study; (2) false positive-positive result in the FNAC but not histologically confirmed; (3) true negative-negative result in the FNAC (i.e., benign) and no carcinoma in the histological study; and (4) false negative-negative result in the FNAC but with a PTC revealed in histological study. Sensitivity was the proportion of patients with PTC and a positive result in the FNAC. The formula used for sensitivity was  $S=TP/(TP+FN)$ , where  $S$ =sensitivity,  $TP$ =true positive, and  $FN$ =false negative. Specificity was the proportion of patients without PTC but a positive result from FNAC. The formula for specificity was  $SP=TN/(TN+FP)$ , where  $SP$ =specificity,  $TN$ =true negative, and  $FP$ =false positive. Positive predictive value (PPV) was the proportion of patients with a positive result and histological confirmation, and the formula was  $PPV=TP/(TP+FP)$ . Negative predictive value (NPV) was the proportion of patients with negative results and without PTC in the histological study, and the formula was  $NPV=TN/(TN+FN)$ . Finally, diagnostic accuracy (DA) was the proportion of patients correctly diagnosed by FNAC, and the formula was  $DA=(TP+TN)/(FP+FN+TP+TN)$ .

All data were verified prior to encoding into Microsoft Excel 2007 worksheet. Statistical analyses were done using Predictive Analysis Software version 18.0 (SPSS, IBM, Chicago, Illinois). Data were presented as mean, standard deviation, and percentage distribution. Categorical correlations were done using chi-square test and continuous variables by independent t-test. Calculations of specificity, sensitivity, PPV, and NPV were done using the formulas stated above.

## Results

A total of 275 patients with thyroid FNAC and final histopathology specimens were reviewed and analyzed. The mean age of the patients was  $38.5 \pm 12.6$  years (range: 14-90 years). Two hundred forty specimens (87.6%) were from the female patients, and 35 (12.4%) were from the male patients. See table 1 for the details of cytology results and histopathological diagnosis.

The histological diagnosis of 179 patients with benign FNAC included 159 (88.8%) benign lesions, 10 (5.6%) PTCs, of which 9

(90%) of the nodules were large (>3.8 cm) and 1 lesion was 2.2 cm. Nine cases (5.0%) were micro-PTC and 1 (0.6%) was FTC. Of the 60 FNAC cases of atypia of undetermined significance or follicular lesion of undetermined significance, 38 (63.3%) were benign, 10 (16.7%) were PTC, 8 (13.3%) were micro-PTC, 3 (5.0%) were FTC, and 1 (1.7%) was MTC. Of 15 cases diagnosed as follicular neoplasm or suspicious of a follicular neoplasm by FNAC, 6 (40.0%) were benign by histopathology, 4 (26.7%) were PTC, 3 (20.0%) were FTC, 1 (6.7%) was micro-PTC, and 1 (6.7%) was HCC. Of the 6 cases suspicious for PTC by FNAC, 1 (16.7%) turned out to be benign by histopathology, and the remaining 5 cases (83.3%) were PTCs. Of the 15 FNAC cases that were consistent with PTC, all turned out to be PTC by histopathology (Table 1).

The analysis of diagnostic accuracy including sensitivity, specificity, PPV, and NPV included a total of 190 cases as we labeled benign FNAC results as negative, PTC or suspicion of PTC was labeled as positive other FNA results were excluded. We excluded 9 micro-PTC cases and one FTC case from benign FNAC group and end by 169 cases. We included 15 FNAC cases with PTC and 6 cases with suspicious of PTC results. Our study yielded 20 true-positive results, 1 false-positive result, 10 false-negative results, and 195 true-negative results. 9 out of 10 false negative results were for nodules size between 3.8 to 6 cm, and one 2.1 cm.

Analysis of the FNAC results obtained were compared with the histological findings in order to rule out malignancy yielded a sensitivity (95% CI) of 66.7% (60.5% to 74.1%), specificity of 99.4% (97.5% to 100%), PPV of 95.2% (91.1% to 97.9%), NPV of 94.1% (90.9% to 97.7%), and a diagnostic accuracy of 94.2% (90.8% to 97.6%) (Table 2).

## Discussion

The literature reports FNAC sensitivity ranging between 55% and 83%, and specificity between 74% and 98%. Our study yielded a sensitivity of 66.7% with a high specificity, PPV, NPV, and diagnostic accuracy (99.4%, 95.2%, 94.1%, and 94.2%, respectively), which is in accordance with values reported in the literature (5,9-11). In contrast to the number of false negatives, the number of false positives was very low ( $n=1$ ). FNAC provides a diagnosis of PTC with high confidence. Any patients with an FNAC result consistent with PTC or suspicious for

Table 1. Distribution of thyroid lesions diagnosed by FNAC versus histopathology

		FNAC results					Total
		Benign	Atypia/follicular lesion	Follicular neoplasm	Suspicious for PTC	Consistent with PTC	
		179 (65.1%)	60 (21.8%)	15 (5.4%)	6 (2.2%)	15 (5.4%)	275
Histopathology diagnoses	Benign	159 (88.8%)	38 (63.3)	6 (40.0%)	1 (16.7%)	0	204 (74.2%)
	PTC	10 (5.6%)	10 (16.7%)	4 (26.7%)	5 (83.3%)	15 (100%)	44 (16.0%)
	Micro-PTC	9 (5.0%)	8 (13.3%)	1 (6.7%)	0	0	18 (6.5%)
	FTC	1 (0.6%)	3 (5.0%)	3 (20.0%)	0	0	7 (2.5%)
	MTC	0	1 (1.7%)	0	0	0	1 (0.4%)
	HCC	0	0	1 (6.7%)	0	0	1 (0.4%)

FNAC: Fine needle aspiration cytology. PTC: Papillary thyroid cancer. FTC: Follicular thyroid cancer. MTC: Medullary thyroid carcinoma. HCC: Hürthle cell carcinoma

**Table 2. Fine-needle aspiration cytology results compared with final histopathology diagnoses**

Histopathology	FNAC		Total
	PTC or suspicious for PTC	Benign	
Papillary thyroid carcinoma (PTC)	20 (66.7%)	10 (33.3%)	30
Benign adenoma	1 (0.6%)	159 (99.4%)	160

Note: We exclude all FNAC results of Atypia and follicular lesion, and Follicular neoplasm. We included 190 cases; 169 FNAC results were benign and 21 were PTC and suspicious for PTC. Final histopathology revealed 160 benign cases and 30 PTC cases

PTC should be referred for surgery, and the initial surgery is usually total thyroidectomy. However, the decision is influenced by the evaluation of the patient's clinical status, the size and aggressiveness of the PTC, and whether radioiodine ablation is planned (3,15).

Our study showed 10 cases of false-negative FNAC results, which may have lowered the sensitivity of the result (66.7%). The majority of these false negatives (9 out of 10) were nodules larger than 3.8 cm in size (3.8 to 6 cm). Although false-negative results in FNAC can be due to sampling error or misinterpretation of cytology slides, the rate of false-negative FNAC reports ranges from 1% to 31% (16,17). Some studies reported an increase in the false-negative rate with larger-sized thyroid nodules (8,19).

The rate of FNAC results of atypia of undetermined significance or follicular lesion of undetermined significance was 21.8%, this should be minimized to represent only 7% of all thyroid FNA biopsy interpretations (14). In our report, the percentage of PTC from this category was 23.3%, which is higher than the reported percentage, which lies between 5% and 10%. (13,19) In patients with an FNAC result of atypia of undetermined significance or follicular lesion of undetermined significance, a 123I scan may be considered if the serum thyrotropin (TSH) level is within the low or low-normal range (normal range, 0.25 to 5.0 IU/mL) . If the scan shows a hot nodule, clinical follow-up with repeat FNA biopsy in 3 to 6 months is appropriate. If the scan shows a cold nodule, the patient should be referred for surgery. If the TSH level is high or high-normal, patients should be advised to repeat FNA biopsy in 3 months, and if FNAC repeatedly shows the same result, patients should be advised to undergo surgery because a significant proportion of them eventually harbor malignancy (15).

In 26.7% of FNAC cases with follicular neoplasm or suspicion of follicular neoplasm, PTC was diagnosed, which agrees with values reported in the literature (13,19,20). A referral for operative exploration is recommended in such cases; usually, a hemi-thyroidectomy or lobectomy is performed, followed by histologic examination for capsular and vascular invasion to distinguish between follicular adenoma and follicular carcinoma (13,15).

There were 7 cases of FTC. One arose from nodules with benign FNAC, 3 had atypia or follicular lesion by FNAC, and 3 had follicular neoplasm or suspicious for a follicular neoplasm by FNAC. In two cases, one was HCC and the other one was MTC, and both had an FNAC finding of follicular neoplasm. HCC and MTC are rare entities. A high index of suspicion coupled with a careful investigation by clinicians and pathologists is needed to make a diagnosis of MTC (21).

### Summary and Recommendation

FNAC as a screening tool for the diagnosis of thyroid nodules had very high diagnostic accuracy (94.2%) in our report and concurred with the standards and the published literature. FNAC should be performed and interpreted by individuals who have adequate training and

experience in performing thyroid biopsy and slide preparation and in reading cytology slides to avoid false negative results. Due to a high proportion of false-negative FNAC results of the large nodules, they may be considered for surgical removal in the presence of other high risk features.

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