

# Discordance between fine needle aspiration biopsy cytology and final histopathology of thyroid nodules according to the Bethesda system

## Bethesda raporlama sistemine göre tiroid nodüllerinde sitopatolojik ve histopatolojik uyumsuzluk

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### Abstract

**Aim:** Fine needle aspiration (FNA) is the most preferred procedure in the preoperative evaluation of euthyroid patients with thyroid nodules. In 2007, the National Cancer Institute recommended the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). The objective of this study was to analyse the correlations between FNA cytology and histopathology results and to determine the accuracy of FNA in the diagnosis of thyroid nodules by using this new reporting system.

**Materials and methods:** We reviewed the medical records of patients who underwent thyroidectomy between January 2006 and March 2010. The records included data on FNA biopsy results and results of the final histologic diagnosis. All FNAs were classified prospectively into unsatisfactory, benign, indeterminate (atypia of undetermined significance, follicular lesion of undetermined significance), follicular neoplasm (FN), suspicious for malignancy and malignant. FNA findings were compared with histopathological examination results. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNA were calculated.

**Results:** FNA was performed in 158 patients. FNA was reported as unsatisfactory in 3 patients, benign in 130 patients, indeterminate lesion in 6 patients, false negative in 6 patients, suspiciously malignant in 2 patients

### Özet

**Amaç:** İnce iğne aspirasyon biyopsisi (İİAB) ötiroid nodüllerin değerlendirilmesinde en sık tercih edilen uygulamadır, fakat tanısal terminolojideki farklılıkların yanı sıra kendisinden kaynaklanan sınırlamaları da vardır. 2007'de ABD Ulusal Kanser Enstitüsü tiroid sınıflaması için Bethesda sınıflamasını önermiştir. Bu çalışmanın amacı İİAB sonuçları ile histopatolojik sonuçların korelasyonunu analiz etmek ve bu yeni sınıflamayı kullanarak tiroid nodüllerinin tanısında İİAB'nin doğruluğunu araştırmaktır.

**Gereç ve yöntem:** Ocak 2006-Mart 2010 arasında yapılan bütün tiroidektomi olguları retrospektif olarak incelendi. İİAB ve histopatoloji sonuçlarını içeren patoloji sonuçları değerlendirildi. Bütün İİAB sonuçları yetersiz, benign, folliküler lezyon, folliküler neoplazm, şüpheli malign ve malign olarak sınıflandırıldı. İİAB sonuçlarının histopatoloji sonuçları ile korelasyonu değerlendirildi. İİAB'nin sensitivite, spesifisite, pozitif prediktif değeri, negatif prediktif değeri ve doğruluğu değerlendirildi.

**Bulgular:** İİAB 158 hastada uygulandı. İİAB sonuçları 3 hastada yetersiz, 130 hastada benign, 6 hastada folliküler lezyon, 6 hastada folliküler neoplazi, 2 hastada şüpheli malign ve 11 hastada malign olarak rapor edildi. İİAB'nin sensitivite ve spesifisitesi %82 ve %96 idi.

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**Başvuru tarihi | Submitted on:** 04.05.2011

**Kabul tarihi | Accepted on:** 19.08.2011

and malignant in 11 patients. FNA sensitivity and specificity in detecting malignancy was 82% and 96% respectively. Positive predictive value of FNA was 64%; its negative predictive value was 98% and its FNA was 95%.

**Conclusion:** FNA biopsy is a safe, accurate, cost effective and useful tool in the initial evaluation of thyroid nodules. False positive and false negative results constitute the limitations of FNA. The causes underlying the discrepancies between FNA results and the final histopathological diagnoses were found to be within acceptable rates in our institution.

**Keywords:** thyroid nodule, fine needle aspiration cytology, histopathology

İİAB'nin pozitif prediktif değeri %64, negatif prediktif değeri %98 ve doğruluğu %95 olarak bulundu.

**Sonuç:** İİAB, tiroid nodüllerinin başlangıç değerlendirmesinde güvenli, doğru, ucuz ve kullanışlı bir yöntemdir. İİAB'nin yanlış pozitif ve yanlış negatif sonuçları İİAB'nin zayıf noktalarıdır. Bununla birlikte biz kliniğimizin İİAB sitoloji ve histopatoloji sonuçlarının korelasyonunun kabul edilebilir oranlarda olduğunu düşünüyoruz.

**Anahtar sözcükler:** tiroid nodül, ince iğne aspirasyon sitolojisi, histopatoloji

## Introduction

Clinically detectable thyroid nodules occur in 4-10% of the population however, only 5-30% of nodules are malignant<sup>1,2</sup>. With the growing availability of sensitive TSH assays, FNA (fine needle aspiration) biopsy and high resolution ultrasonography (HRUSG), thyroid nodules are being increasingly recognised, diagnosed and treated. Nodules are sometimes picked up on neck imaging for non-thyroid conditions; these so-called incidentalomas also need evaluation to rule out malignancy. Palpable nodules are best evaluated by HRUSG followed by USG-guided FNA. Many authors have recommended FNA as an essential step in the evaluation of the solitary thyroid nodule<sup>3,4</sup>.

USG guided fine needle aspiration biopsy is a minimally invasive and safe method and has become the gold standard in the diagnosis of thyroid pathologies<sup>5,6</sup>. The accuracy of FNA approaches 90% with appropriate technique and interpretation by an experienced cytopathologist<sup>7</sup>. USG guided fine needle aspiration biopsy has led to a substantial decrease in unnecessary thyroidectomy operations while increasing the number of diagnosed cancer patients<sup>8</sup>. Thus FNA cytology findings play a vital role in patient selection for operation. Nevertheless, FNA has some limitations, and both false-positive and false-negative results occur.

The purpose of this study was to evaluate the results of thyroid FNA in our institution and to determine the reasons for discrepancies between the cytological and histological diagnoses.

## Patients and Methods

We performed a retrospective review of all unilateral and bilateral thyroidectomies performed between Janu-

ary 2006 and March 2010 and identified a total of 158 patients with both preoperative FNA cytology information and a final histopathologic report.

Patients with non-toxic, solitary nodules or with multinodular goitre and who had undergone a FNA biopsy of the dominant nodule; were taken into the study. Data were obtained for demographic features, preoperative ultrasonography findings, preoperative FNA cytology, the surgical technique performed and final histopathologic report.

Fine needle aspirations were performed by the same cytopathologist using a 23 or 25 - gauge disposable needle, without local anaesthesia. All FNA procedures were carried out under ultrasound guidance. Smears were prepared by the same cytopathologist, using a two-slide contact-and-smear technique. Smears were fixed in 90% ethanol and stained with either Papanicolaou or hematoxylin and eosin stains. Histopathologic diagnoses were made according to standard practice.

All FNAs were classified prospectively as unsatisfactory, benign, indeterminate [atypia of undetermined significance (AUS), follicular lesion of undetermined significance (FLUS)], follicular neoplasm (FN), suspicious for malignancy and malignant by using the Bethesda thyroid FNA classification system<sup>9</sup>. Inadequate samples were reported as nondiagnostic (ND) or unsatisfactory (UNS). This category applies to specimens that are unsatisfactory owing to obscuring blood, overly thick smears, air drying of alcohol-fixed smears, or having an inadequate number of follicular cells. Fewer than six clusters of cells on each of the two slides obtained from thyroid aspirates were accepted as inadequate for diagnosis<sup>10</sup>. FNA cytology was repeated in patients with inadequate sampling.

Postoperative cytology results were categorised into two groups as benign (benign colloid nodule, follicular adenoma, Hashimoto thyroiditis, hurtle cell adenoma, hyperplasia and thyroiditis), malignant (papillary carcinoma, follicular carcinoma, medullary carcinoma, anaplastic carcinoma, lymphoma and metastatic disease).

Results with benign FNA cytology and with final histopathology showing a carcinoma were regarded as false negative; and results with malignant FNA cytology and benign final histopathology were regarded as false positive. The sensitivity, specificity, positive and negative predictive values and accuracy of FNA biopsy were calculated by comparing with final histopathology.

Some patients with benign FNA results underwent total or partial thyroidectomy according to other specific indications, including a very large goiter, compression or tracheal deviation, enlarging nodule, cold nodule on scintigraphy and patient's request. Patients assessed as having indeterminate lesions, follicular neoplasms or suspicion for malignancy on FNA were presented with the option of undergoing either a unilateral or bilateral thyroidectomy. For those patients who chose to undergo an initial unilateral or bilateral thyroidectomy and the final pathology report proved the lesion to be malignant, completion to total thyroidectomy was subsequently accomplished. Patients diagnosed as malignant by FNA biopsy underwent total thyroidectomy.

## Results

Medical records of 158 patients who underwent a thyroidectomy operation between January 2006 and

March 2010 were evaluated retrospectively. Of these patients; 132 were female and 26 male. The median age at first presentation was 45 years (range; 20-75). The mean diameter of the dominant nodule chosen for FNA was  $3.18 \pm 1.63$  cm. FNA biopsy results were assessed as unsatisfactory in 3 patients (2%), benign in 130 (82%), indeterminate in 6 (4%), follicular neoplasm in 6 (4%), suspicious for malignancy 2 (1%), and malignant in 11 (7%), according to FNA cytology. FNA cytology was repeated in 8 patients with inadequate sampling and 5 of these patients were diagnosed as benign colloid nodule. FNA cytology of 3 patients remained persistently unsatisfactory.

Bilateral thyroidectomy was performed in 110 patients and 48 patients underwent unilateral thyroidectomy. Of the patients initially undergoing bilateral or unilateral thyroidectomy, 12 patients required completion to total thyroidectomy because of carcinoma detected in the histopathological examination of the initially resected lobe.

Correlation of cytological diagnosis by FNA cytology with the final histological diagnosis is shown in table I. Of the 130 patients with a benign FNA cytology, 5 were found to have carcinoma on final pathology (false negativity 4% and sensitivity 82%). FNA cytology indicated a malignant diagnosis in 11 cases, but the final histological assessment was benign in 2 of these cases (false positivity 18% and specificity 96%). In 6 cases, an indeterminate diagnosis was made and the definitive histological diagnosis was malignant in 3 of these cases (50%). The positive predictive value of a malignant

**Table 1:** Correlation of FNA cytology with final histopathology

Results of FNA biopsy	Results of Histopathology						
	Papillary carcinoma	Follicular carcinoma	Benign colloid nodule	Hashimoto thyroiditis	Hurtle cell adenoma	Follicular adenoma	Lymphocytic thyroiditis
Unsatisfactory or nondiagnostic (n=3)							
Benign colloid nodule (n=130)	4	1	113	4		6	5
Indeterminate (n=6) (atypia and follicular lesion)	3		2		1		
Follicular neoplasm (n=6)	2	1	3				
Suspicious for malignancy (n=2)	1				1		
Malignant (n=11)	9				1		1
<b>Total (n=158)</b>	<b>19</b>	<b>2</b>	<b>118</b>	<b>4</b>	<b>3</b>	<b>6</b>	<b>6</b>

FNA was 64%, the negative predictive value of a benign FNA was 98%. The overall accuracy was 95%.

## Discussion

In the general population, thyroid nodules are found in 5% by palpation and in 50% by ultrasonography (US)<sup>11</sup>. FNA biopsy is the most accurate and cost-effective diagnostic method for evaluating a patient with a thyroid nodule<sup>12-14</sup>.

FNA is one of the most widely used investigative tools in medicine. It is especially important to confirm the diagnosis preoperatively; to allow for planning and decision making in surgery. Although the indication for surgery is never based on the outcome of a single test alone, the results of FNA biopsy play a major role in the decision making process. False-positive interpretations lead to unnecessary thyroidectomy while false-negative results lead to delayed surgical treatment, which may result in higher morbidity and mortality<sup>15</sup>.

Dyspnea, dysphagia, hoarseness, rapid increase in nodule size, fixation of the nodule to surrounding tissues and presence of lymphadenopathy; are findings suggesting malignancy. Radiologic imaging and FNA biopsy findings are helpful in the management of thyroid nodules. Nodule size, characteristics of the nodule (solid, cystic, cystic with solid component), hypoechogenicity, irregularity of margins, presence of calcifications and invasion of surrounding tissues are important ultrasonographic findings in favor of thyroid malignancy<sup>16</sup>. Thyroid function tests or scintigraphy are also helpful for deciding the functional condition of thyroid nodules, but these procedures are less cost-effective, less specific and sensitive, when compared to FNA<sup>17</sup>. Malignancy was observed in 6-20% of thyroid nodules which were evaluated as cold on scintigraphy, but only 1-2% of hot nodules were malignant<sup>18</sup>. Currently, assessment and follow up of thyroid nodules with USG and FNA under ultrasonographic guidance is the gold standard treatment modality. The accuracy of FNA cytology depends on the characteristics of the target lesion, aspiration technique and the experience of the cytopathologist<sup>15,19-21</sup>.

The main limitation of FNA is unsatisfactory sampling, which gives misleading results. In our study, unsatisfactory FNA cytology rate was as low as 2%. Insufficient cellular material from cystic or haemorrhagic lesions, the experience of cytopathologists in performing the FNA, the number of punctures, and the technique of preparing smears all affect the rate of misleading results<sup>20</sup>. If the smear is insufficient, aspirations could be repeated immediately. This would help to reduce the number of inadequate smears.

The accuracy of fine-needle aspiration biopsy for malignancy can be estimated by calculating its sensitivity (true-positive results are divided by true-positive plus false-negative results) and specificity (true-negative results divided by true-negative plus false-positive results). The estimation of sensitivity and specificity depend on how the indeterminate category and suspicious for malignant results are handled. If suspicious cytologic results are considered as positive, then sensitivity will increase and specificity will decrease. On the other hand, if the suspicious results are considered as negative, specificity will increase and sensitivity will decrease. In our study, indeterminate and suspicious for malignant cases were evaluated apart from the malignant or benign groups. Our current experience indicated the sensitivity, specificity and accuracy of FNA to be 82%, 96% and 95%, respectively. If we added the indeterminate cases and those suspicious for malignancy into the group of cases definitely malignant, the sensitivity rate would be 89%. Hamburger reported a sensitivity and specificity of 85% and 80%, respectively and he used a FNA malignancy category which included both definitely malignant and suspicious for malignancy. This wide definition of positive FNA causes a decrease in the false negative rate and consequently increases the sensitivity<sup>22</sup>.

In 1993, Gharib et al reviewed the results of 18183 FNAs. They reported sensitivity and specificity, positive predictive value, negative predictive value, and false negativity results as 83%, 92%, 81%, 96% and 5% respectively<sup>8</sup>. Our results of FNA compare favorably with results reported of Gharib.

Baloc et al<sup>7</sup> reviewed the results of 662 FNA and reported a sensitivity and specificity of 92% and 84, respectively. Morgan et al reported the sensitivity, specificity, positive predictive value, negative predictive value, false positivity and false negativity of FNA cytology in their study as 55%, 74%, 70%, 67%, 26%, 46% respectively. The accuracy of FNA cytology was 67%<sup>23</sup>.

Incorrect sampling, sampling difficulty in occult lesions, presence of tumor in a nodule other than the biopsied one and difficulty in the differentiation between neoplasm and cancer with cytopathology; are the causative factors of false negative and false positive results.

False-negativity rate is defined as the percentage of patients with benign cytologic findings who are confirmed to have malignant lesions of the thyroid. In our series, of patients with FNA cytology negative for malignancy, only five were found to have malignancy. We found false negativity rate as 4%. In our series, the false negative rate was high. But it was lower than the rates reported by Morgan et al.<sup>23</sup> In our three patients with carcinoma, carcinoma was detected in only a relatively small

focus of the adenomatous nodule. This was thought as the probable cause of false negativity. However the most common pitfalls for false-negative diagnoses consisted of suboptimal material and underdiagnosis of papillary carcinoma due to cystic degeneration<sup>24</sup>. In our two patients with carcinoma, the carcinoma was detected in the cystic degenerated nodule.

The false-positivity rate is the percentage of patients with "malignant" fine-needle aspirates who are found to have benign lesions at surgery. False-positive reports do not constitute a major problem with fine-needle aspiration. The false-positivity rate was 18% in our study. These results are similar to the results reported by Layfield et al.<sup>25</sup> Gharib and colleagues reported that the false positivity rate varied from 0% to 7.7%<sup>8</sup>. In our study, the most common pitfall for false positive cases was overdiagnosis and misdiagnosis of hürtle cell adenoma and lymphocytic thyroiditis.

In the present study the positive predictive value for malignancy obtained by FNA cytology was 81%, compared to other studies where it ranged from 37.7-100%. The positive predictive value depends on the technique and experience of the physicians and how the data are interpreted. FNA cytology of the thyroid has a high negative predictive value, which is useful to reassure the majority of patients presenting with thyroid enlargement. In the present study the negative predictive value of FNA cytology was 96%, comparable to other reported values which range between 69.2% and 97.1%<sup>26-29</sup>.

However, a negative FNA should never exclude malignancy if there is a strong clinical suspicion. Indeterminate FNA cytology findings were due to difficulty in differentiating benign follicular and Hürtle cell growths from their malignant counterparts<sup>8</sup>. The diagnosis of follicular and Hürtle cell carcinoma requires identification of capsular or vascular invasion, which is impossible with an FNA cytology specimen<sup>26</sup>. The entire lobe containing the neoplastic lesion must be removed and examined for vascular or capsular invasion and cellular characteristics to prove malignancy.

Cytologic nuclear atypia consistent with a follicular neoplasm confers a high risk of cancer. Patients having a FNA cytology diagnosis of atypical cell and follicular cell lesions should be advised to undergo surgery, as a significant proportion harbour malignancy.

In the case of indeterminate FNA results, most authors suggest that the patient should undergo lobectomy (as an initial approach), near-total or total thyroidectomy because of the possibility of capsular or vascular invasion and the uncertain natural history of these nodules<sup>30-33</sup>. Although FNA is a specific first-line test, up to 30% of patients with nodular thyroid disease will receive an FNA result which reports a follicular lesion or a suspicious one<sup>33</sup>. In our study, 50% of patients with inde-

terminate cytology and follicular neoplasm were diagnosed as having malignancy with histopathology.

During the last decade, to avoid unnecessary thyroidectomy, many studies have searched for predictors of malignancy for indeterminate cytology. In these studies, a diameter larger than 3 cm, immobility (fixation) of the mass and young age were found to be the clinical findings associated with a malignant nodule<sup>24,34,35</sup>.

Chang et al. suggested that intraoperative frozen section is a valuable procedure for identifying malignancies in cases with an indeterminate or unsatisfactory cytological diagnosis<sup>35</sup>. Yah et al suggested a repeated evaluation of the sample in lesions reported as suspicious. This could change the surgical management in some patients<sup>36</sup>.

In our study, in all patients with indeterminate cytology, the decision on operative technique was based on intraoperative frozen section examination results and on clinical findings. Frozen section in thyroid surgery is used to make an intraoperative pathological diagnosis of malignancy in a thyroid nodule at the time of hemithyroidectomy. A positive diagnosis allows completion of thyroidectomy, thus avoiding reoperation.

In conclusion, FNA diagnosis of thyroid nodules is a helpful method for selection of patients for surgery and has become an important examination technique for the initial evaluation of thyroid nodules. Although a carefully taken history, together with clinical and radiologic findings help to stratify the risk of malignancy, FNA cytology constitutes the cornerstone of diagnosis. False positive and false negative results are the drawbacks of FNA cytology. This report shows that the discrepancies between the cytological and histological diagnoses were within acceptable rates in our institution.

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