Role of Fine Needle Aspiration Cytology and Intraoperative Diagnosis in the Diagnosis of Thyroid Nodules

Tiroid Nodüllerinin Tanısında İnce İğne Aspirasyon Sitolojisi ve İntraoperatif Tanı Yönteminin Rolü

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ABSTRACT

Objective: The utilization of fine needle aspiration cytology-FNAC is an accurate, cost-effective and specific first method in the diagnosis of thyroid nodules. However, cases diagnosed as "inadequate for interpretation" or "suspicious cytology" remain a dilemma. Intraoperative diagnosis (frozen section) is usually performed to avoid unnecessary surgical treatment. The aim of this study was to assess the sensitivity, specificity, and accuracy of FNAC and intraoperative section for the diagnosis of thyroid nodules.

Material and Method: The present study included 291 consecutive patients who underwent FNAC, intraoperative section and subsequently surgery.

Results: Of 291 FNAC specimens, 213 were benign and 31 were suspicious, 25 were positive for malignancy, and 22 were nondiagnostic. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of FNAC in the diagnosis of malignancy were 43%, 68%, 80%, 72%, and 73%, respectively. No false positive results were noted. Of 291 patients analyzed by intraoperative section, the diagnosis was benign in 186 and positive for malignancy in 67 patients. Thirty-eight patients were diagnosed using permanent sections. Of these 38 patients, 21 had malignant tumors confirmed by the permanent sections. False-positive results were noted in only one case. The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of intraoperative diagnosis were 76%, 82%, 82.8%, 85%, and 84.5%, respectively.

Conclusion: FNAC is a sensitive first diagnostic method in selecting patients who require surgery. Routine use of intraoperative section is specific and complementary in determining the extent of surgery in patients with suspicious or malignant cytology.

Key Words: Fine needle aspiration, Cytology, Thyroid, Intraoperative diagnosis

ÖZ

Amaç: Tiroid nodüllerinin tanısında ince iğne aspirasyon sitolojisi-İİAS doğru, ucuz ve spesifik bir ilk tanı yöntemidir. Ancak, yetersiz ve kuşkulu tanı alan olgular problem yaratmaktadır. Bu olgularda gereksiz bir geniş cerrahi girişimin önlenmesi için genellikle intraoperatif tanı yöntemi uygulanmaktadır. Çalışmamızda, tiroid nodüllerinin tanısında İİAS ve intraoperatif tanı yöntemi uygulamanın duyarlılık, özgüllük ve tanısal doğruluğunun değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya, İİAS, intraoperatif tanı ve ameliyat materyalleri olan 291 olgu alındı.

Bulgular: İki yüz doksan bir İİAS olgusunun 213'ü benign, 31'i kuşkulu, 25'i malign ve 22'si yetersiz idi. İİAS'nin duyarlılık, özgüllük, tahmini pozitif değeri, tahmini negatif değeri ve tanısal doğruluk oranı sırasıyla %43, %68, %80, %72 ve %73 idi. Yanlış pozitif sonuç hiç yoktu. İntraoperatif tanı yöntemi uygulanan 291 olgunun 186'sı benign, 67'si malign olarak değerlendirildi. 38 olguda tanı parafin kesitlerde verildi. Bu olguların 21'i histolojik olarak malign tanısı aldı. Yanlış pozitif sonuç sadece bir olguda saptandı. İntraoperatif tanının duyarlılık, özgüllük, tahmini pozitif değeri, tahmini negatif değeri ve tanısal doğruluk oranı sırasıyla %76, %82, %82.8, %85 ve %84,5 olarak bulundu.

Sonuç: İİAS, cerrahiye gidecek olguların seçiminde duyarlı bir ilk basamak tanı yöntemidir. İntraoperatif tanı yönteminin kullanımı ise kuşkulu ve malign sitoloji tanısı alan olguların operasyon şekline kararda, spesifik ve tamamlayıcı bir uygulamadır.

Anahtar Sözcükler: İnce iğne aspirasyonu, Sitoloji, Tiroid, İntraoperatif tanı

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INTRODUCTION

Thyroid nodules are quite frequent lesions and seen in 4-7% of the population (1). However, the incidence of malignancy in thyroid nodules is known to be 5 to 30% (2,3). Surgery is used for malignant nodules and large symptomatic nodules. A systematic approach is therefore needed for evaluation of thyroid nodules in order to prevent mistaken and unnecessary surgery (4). Fine needle aspiration cytology (FNAC) is an easy, inexpensive and very reliable primary method for preoperative evaluation (3,5,6). The aim of this method is to define nodules that will require surgical treatment and to prevent unnecessary surgery of benign lesions. Although FNAC has high diagnostic value, the approach to 10% of patients who have inadequate cytology and 15% with suspicious cytological diagnosis is quite controversial (8-10). Repeated FNAC is suggested for cases with a diagnosis of inadequate cytology. Most cases that receive a diagnosis of suspicious cytology have a hyperplastic nodule, follicular adenoma, follicular carcinoma or papillary carcinoma follicular variant, named "follicular lesion" or "follicular neoplasia" (11). Intraoperative diagnosis may be used especially for these cases to obtain a histological evaluation and decide on the best surgical approach (12). This technique is highly specific diagnostically but there are conflicting reports on its routine use. Some investigators support the use of routine intraoperative diagnosis with FNAC results (13-15), while others favor limited use of this procedure taking the expense and time limitation during surgery into account (16-18).

Our aim in this study was to determine the role, specificity and sensititivity of preoperative thyroid FNAC and intraoperative diagnosis for thyroid nodules by comparing the results of cases where these methods were used with histopathological diagnoses.

MATERIAL and METHOD

A total of 457 FNAC and 515 intraoperative diagnostic procedures were used for the thyroid material investigated at our Department between January 2000 and March 2008. We included 291 cases where there was a FNAC and intraoperative diagnostic sample and the operative material had been evaluated at our department.

All thyroid FNAC material was obtained at the Radiology or Endocrinology Departments of our University and sent to our Department after being air-dried and fixated on slides with alcohol. The air-dried slides were stained with the May - Grünwald-Giemsa stain while the alcohol-fixated slides were stained with hematoxylin-eosin and the results were reported after screening by cytopathologists (AV, DN). FNAC material adequacy was accepted when at least 8-10 follicular epithelial cell clusters were found. The FNAC reports were as follows:

1. Benign cytology (colloid or adenomatous nodules, hyperplastic nodules and thyroiditis)
2. Malignant cytology (papillary, medullary, anaplastic carcinoma or unspecified type)
3. Suspicious cytology (smear contains atypical cells but inadequate for diagnosis, cellular follicular nodule)
4. Inadequate cytology (material inadequate for diagnosis, technical problems).

A sample was taken from the most macroscopically suspicious nodule among the thyroid surgery material for the intraoperative diagnostic sectioning. The number of samples was 2 for nodules 2 cm in size or smaller and 3 for larger nodules. The sectioning was from areas with possible macroscopic capsule invasion for encapsulated nodules as it would not be possible to evaluate the whole nodule during intraoperative diagnosis. Intraoperative sections were stained with hematoxylin-eosin and evaluated. Intraoperative diagnostic evaluation results were provided to surgery as follows:

1. Benign (colloid or adenomatous nodules, hyperplastic nodules and thyroiditis)
2. Malignant (papillary, papillary–follicular variant, medullary, anaplastic carcinomas)
3. Suspicious (follicular neoplasia where a definite diagnosis could not be reached on capsule evaluation, Hurthle-cell neoplasia).

The histopathological diagnosis was provided after the surgery material from thyroid was evaluated by two pathologists (MT, YE) following re-analysis and sampling.

The FNAC and intraoperative diagnosis results were compared with the histopathological diagnoses:

True positive: Positive for malignancy also proven histologically

True negative: Negative for malignancy also proven histologically

False positive: Positive for malignancy not proven histologically

False negative: Negative for malignancy not proven histologically

Sensitivity: True positive/True positive + False negative

Specificity: True negative/False negative + False positive

Estimated positive value: True positive/True positive + False positive

Estimated negative value: True negative/True negative + False negative

Diagnostic accuracy: True positive + True negative/True positive + True negative + False positive + False negative

Analysis of statistical comparisons was performed by the SPSS (Statistical Package for the Social Sciences, version 15.0) software.

RESULTS

Evaluation of the 291 cases with FNAC revealed 213 cases (72%) with benign cytology, 25 cases (9%) with malignant cytology, 31 cases (11%) with suspicious cytology and 22 cases (8%) with inadequate cytology (Figure 1) The intraoperative diagnosis was benign in 186 cases (64%), malignant in 67 (23%) and suspicious in 38 (13%) (Figure 2). The histopathological diagnosis was benign in 177 cases (61%) and malignant in 114 (39%) (Figure 3). Distribution of 126 cases with a benign histopathological diagnosis were as follows: 36 cases of thyroiditis, 1 diffuse hyperplasia, 1 Hurthle-cell follicular adenoma and 13 cases of thyroid tissue. Distribution of 114 cases with a malignant histopathological diagnosis were as follows: 47 cases of papillary carcinoma, 17 papillary carcinoma follicular variant, 6 medullary carcinoma, 2 poorly-differentiated thyroid carcinoma and 1 case of follicular carcinoma.

Correlation of FNAC and histopathological diagnosis

213 cases that had preoperatively received a diagnosis of benign or malignant cytology with FNAC were histopathologically also benign in 153 (72%) and malignant in 60 (28%) cases. 31 cases that had received a diagnosis of suspicious cytology were histopathologically benign in 11 (35.5%) and malignant in 20 (64.5%). None of the cases with malignant FNAC diagnosis were benign histopathologically (0%) and all 25 cases were found to be malignant (100%) (Table I).

Of the 11 cases that had a suspicious cytology before surgery but received a diagnosis of benign histopathology, 6 were thyroiditis, 4 nodular goitre and 1 Hurthle-cell adenoma (Table II).

Of the 60 cases that had been evaluated as benign cytology before the surgery but the histopathological diagnosis was malignant, 15 were classic papillary carcinoma, 32 papillary microcarcinoma, 10 papillary carcinoma follicular variant, 1 follicular carcinoma and 2 medullary carcinoma (Table III). Of the 20 cases that had been evaluated as suspicious cytology but received a malignant histopathological diagnosis, 10 were classical papillary carcinoma, 5 papillary carcinoma follicular variant, 3 papillary microcarcinoma and 2 poorly differentiated thyroid carcinoma (Table III).

The group with suspicious cytology was included in the malignant group for statistical analysis due to the effect on surgical decision stage and the higher number of malignant

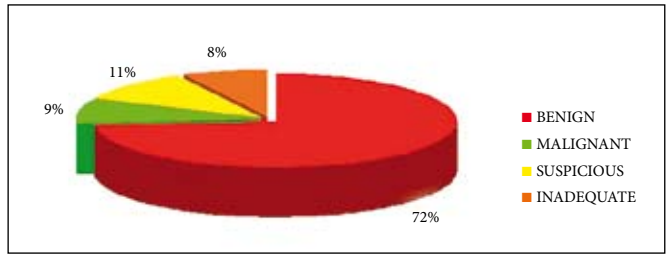

Figure 1: Distribution of FNAC results.

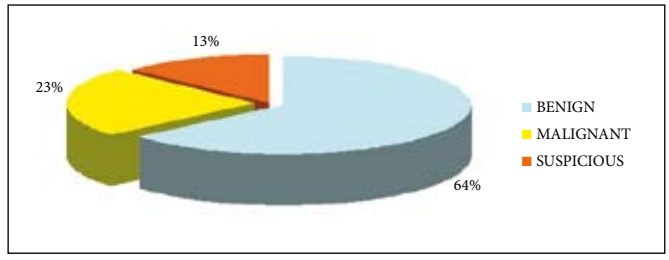

Figure 2: Distribution of intraoperative results.

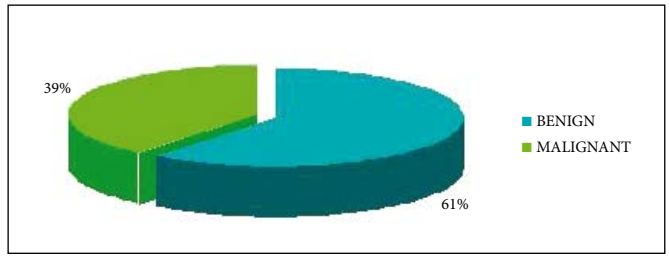

Figure 3: Distribution of histopathological results.

Table I: Correlation of FNAC and histopathological diagnosis

CYTOLOGY	HISTOPATHOLOGICAL DIAGNOSIS	
	BENIGN (number of cases /%)	MALIGNANT (number of cases/%)
BENIGN	153 (72%)	60 (28%)
SUSPICIOUS	11 (35.5%)	20 (64.5%)
MALIGNANT	0 (0%)	25 (100%)

results (64.5%) from histopathological diagnosis. This gives the following values for preoperative FNAC in the diagnosis of thyroid nodules: sensitivity 43%, specificity 68%, positive predictive value 80%, negative predictive value 72% and diagnostic accuracy rate 73%. The false negative rate was 28% while the false positive rate was 0%.

Correlation of intraoperative diagnosis and histopathological diagnosis

The histopathological diagnosis was benign in 159 of the 186 cases with a benign diagnosis on intraoperative diagnosis while 27 were malignant. Of the 38 paraffin-embedded tissues, 17 were histopathologically benign and 21 were malignant. Only one of the 67 cases reported malignant was histopathologically benign while 66 were malignant (Table IV).

Table II: Correlation of FNAC and benign histopathological diagnosis

BENIGN HISTOPATHOLOGICAL DIAGNOSIS		BS	KS	MS	Inadequate
Nodular goitre		112	4	0	10
Thyroiditis		30	6	0	0
Hurthle cell follicular adenom		0	1	0	0
Diffuse hyperplasia		1	0	0	0
Other		10	0	0	3
Total	177	153	11	0	13

BS: Benign cytology, KS: Suspicious cytology, MS: Malignant cytology

Table III: Correlation of FNAC and malignant histopathological diagnosis

MALIGNANT HISTOPATHOLOGICAL DIAGNOSIS		BS	KS	MS	Inadequate
Papillary carcinoma		15	10	17	5
Papiller microcarcinoma		32	3	3	3
Papillary carcinoma follicular variant		10	5	1	1
Follicular carcinoma		1	0	0	0
Medullary carcinoma		2	0	4	0
Poorly differentiated carcinoma		0	2	0	0
Total	114	60	20	25	9

BS: Benign cytology, KS: Suspicious cytology, MS: Malignant cytology

Nine of the 17 cases that had been embedded in paraffin and received a benign histopathological diagnosis had thyroiditis, 7 had nodular goitre and 1 was diffuse hyperplasia. A case reported as false positive received a diagnosis of lymphocytic thyroiditis on histopathology (Table V). Of the 21 paraffin-embedded cases, 10 were diagnosed as papillary carcinoma follicular variant while 6 had papillary carcinoma and 5 classic papillary carcinoma (Table VI).

There were 26 cases evaluated as benign with intraoperative diagnosis but found to be malignant on histopathology and 16 were papillary microcarcinoma, 6 classic papillary carcinoma, 3 papillary carcinoma follicular variant and 1 medullary carcinoma (Table VI).

We performed a statistical evaluation by including the paraffin-embedded group in the malignant group for the intraoperative diagnosis method, due to the same reasons with suspicious FNAC. We found the sensitivity of intraoperative diagnosis method for the diagnosis of thyroid nodules as 76%, with specificity 82%, positive predictive value 82.8%, negative predictive value 85% and diagnostic accuracy rate of 84.5%.

Table IV: Correlation of Intraoperative diagnosis and histopathological diagnosis

INTRAOPERATIVE	HISTOPATHOLOGICAL DIAGNOSIS	
	BENIGN	MALIGNANT
BENIGN	159 (85.5%)	27 (14.5%)
SUSPICIOUS	17 (45%)	21 (55%)
MALIGNANT	1 (1.5%)	67 (98.5%)

Table V: Correlation of intraoperative diagnosis and benign histopathological diagnosis

BENIGN HISTOPATHOLOGICAL DIAGNOSIS		Benign	Suspicious	Malignant
Nodular goitre		119	7	0
Thyroiditis		26	9	1
Hurthle cell follicular adenoma		1	0	0
Diffuse hyperplasia		1	1	0
Other		12	0	0
Total	177	159	17	1

Table VI: Correlation of intraoperative and malignant histopathological diagnosis

MALIGNANT HISTOPATHOLOGICAL DIAGNOSIS		Benign	Suspicious	Malignant
Papillary carcinoma		6	5	36
Papillary microcarcinoma		16	6	19
Papillary carcinoma follicular variant		3	10	4
Papillary carcinoma		1	0	0
Medullary carcinoma		1	0	5
Poorly differentiated carcinoma		0	0	2
Total	114	27	21	66

DISCUSSION

FNAC is a reliable method in widespread use as a primary diagnostic method for the preoperative evaluation of thyroid nodules (3,5,6). It aims to differentiate between benign and malignant samples and prevent unnecessary surgical interventions. A literature search revealed FNAC sensitivity of 69-88% in the diagnosis of thyroid nodules, with a specificity of 45-91%, positive predictive value of 28-71%, negative predictive value of 74-94% and diagnostic accuracy rate of 53-86% (13,18-21). Chao et al. (21) reported a sensitivity of 86.1%, specificity of 59.7% and diagnostic accuracy of 64.6% for FNAC in their 619-case series. Caraci et al. (13) reported FNAC sensitivity of 88%, specificity of 45% and diagnostic accuracy rate of 53% in their 206-case series. Brooks et al. (20) reported FNAC sensitivity of 87%, specificity of 46% and diagnostic accuracy rate of 68% in their 564-case series. Our values were 43% for FNAC sensitivity, 68% for specificity, 80% for positive predictive value, 72% for negative predictive value and 73% for diagnostic accuracy. When compared with other reports, the sensitivity of our series is relatively low but the specificity and diagnostic accuracy values are close to or even better than some other reports. 0% false positive rate in our series is also an important point that needs to be emphasized. The false positivity rate reported in the literature is 0% to 2.5% (22). The series by Chao et al. (21) provides a rate as high as 11.4%.

False negativity rate in FNAC is 0% to 29% in the literature (3,13,19,23-25). Morgan et al. (26) have reported a false negativity rate of 46% in their 253-case study. Our false negativity rate was 28%. Errors in sampling and interpreting nodules are the most important causes of false negative FNAC results (27-29). Repeated FNAC will increase diagnostic accuracy if suspicion continues with a solitary nodule or dominant nodule interpreted as benign cytology. Some investigators prefer routinely using the intraoperative diagnosis methods (30).

The intraoperative diagnosis method is generally thought to have higher specificity in the diagnosis of thyroid nodules (13,20,24,31,32). The reported sensitivity for intraoperative diagnosis is 57-80% while the specificity is 90-99%, positive predictive value is 95-97%, negative predictive value is 74-95% and the diagnostic accuracy rate is 77-96% (13,20,24,31). We found the sensitivity of the intraoperative diagosis method to be 76% for the diagnosis of thyroid nodules while the specificity was 82%, positive predictive value 82.8%, negative predictive value 85% and diagnostic accuracy 84.5%. The higher values of FNAC results indicate that the intraoperative diagnosis procedure is a very specific diagnostic method for the diagnosis of thyroid nodules and for planning the surgery. The changes in follicular epithelial cells in cases accompanied by thyroiditis can lead to interpretation errors. These cellular changes must therefore be considered before making a diagnosis of malignancy during the intraoperative evaluation of cases with thyroiditis. The false positive rate in our series was 0.87% and only one lymphocytic thyroiditis case received a malignant diagnosis with the intraoperative diagnosis method. Nine of the 17 cases embedded in paraffin received a histopathological diagnosis of thyroiditis.

There were one Hurthle-cell follicular adenoma, one follicular carcinoma and 17 papillary carcinoma follicular variant in the group defined as "follicular neoplasia" in our series. This difference in distribution is due to our inclusion of cases with all three materials. The diagnosis of follicular carcinomas is based on capsule and/or vascular invasion (33). FNAC is not suitable for the differential diagnosis of follicular adenoma/carcinoma due to these diagnostic criteria. Some studies suggest not using the intraoperative diagnosis method for these lesions due to its low diagnostic value (19,34,35). However, some investigators suggest imprint analysis as well so that the nuclear details can be better imaged without freezing artifact during intraoperative diagnosis for these lesions (21,36-38).

FNAC is an excellent method in selecting cases that need surgery but it may not be adequate by itself in planning the extent of surgery for some lesions due to its low sensitivity and specificity. The higher specificity of the intraoperative diagnosis method decreases the rate of secondary surgical intervention. The reasons for the low FNAC sensitivity in our series are:

- Different physicians (endocrinologist and radiologist) performing FNAC
- Inclusion of cases with FNAC, intraoperative diagnosis and surgical material
- Presence of microcarcinomas and especially microscopic tumor foci found by chance in our case group.

However, the lack of a false positive result in FNAC and a 0.87% rate for the intraoperative diagnosis method increases our diagnostic accuracy.

In conclusion, each institution should evaluate procedures regarding the preoperative and peroperative approaches to thyroid nodules according to its own technical capacity. We use FNAC preoperatively as the primary method to diagnose thyroid nodules and the intraoperative diagnosis method is always used as a complementary method especially for cases that receive a diagnosis of suspicious cytology.

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