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Evaluation of the FNA Accuracy in Differentiating Malignant from Non- Malignant Thyroid Nodules in Comparison with Postoperative Histopathological Findings

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ABSTRACT

Background and Aim: Thyroid nodules are one of the most common thyroid disorders and due to these nodules have a chance for malignancy, all thyroid nodules should be evaluated cytologically. The choice method for this assessment is fine needle aspiration (FNA). Different studies have reported different values for the diagnostic power of FNA compared to the pathological evaluation of the surgical specimen. In this study, we aimed to evaluate the power of FNA in comparison with postoperative histopathological findings in differentiating malignant thyroid nodules from non-malignant nodules.

Methods: In this diagnostic study, the records of patients with thyroid nodules who required diagnostic FNA based on the findings of clinical examination and diagnosis (ultrasound and TSH) were evaluated. The data of 359 patients with FNA and cytopathology results were assessed based on a surgical specimen.

Results: Of these 359 patients, 279 (77.7%) were women and 80 (22.3%) were men. The mean age of the patients was 43.28 ± 13.37 years. The mean age of patients in the group with benign thyroid nodules was significantly higher than patients with malignant thyroid nodules (P-value = 0.001). For FNA, sensitivity was 74%, specificity was 86%, positive predictive value was 76% and finally negative predictive value was 85%. The accuracy of FNA was 82%.

Conclusion: FNA can be used in most nodules. Of course, accompanying with clinical findings should be considered.

INTRODUCTION

Adults have a 4-7 % chance of developing thyroid nodules. Although only about 5-10% of nodules in adults are cancerous, the majority of nodules are non- neoplastic or benign. Thyroid cancers in thyroid nodules are an important diagnosis that should not be ignored (1-3). Thyroid malignancies are the most common types of endocrine malignancies (4, 5). Cytology and pathology are the gold standard method for thyroid nodules assessment (6). Fine needle aspiration (FNA) is commonly used to evaluate non- toxic nodules as a choice diagnostic technique. Its main goal is to do an evaluation in order to identify patients who need surgery and to choose the

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best surgical techniques for them. FNA can potentially serve as a screening diagnostic tool, depending on the kind of lesion. The goal of FNA as a diagnostic technique is to detect papillary thyroid carcinoma and other cancers (7-9).

FNA is the most cost-effective method among all methods for thyroid nodule assessment but its accuracy for correct diagnosis of the type of nodule is under discussion (10). In most studies on surgical nodules, it has been seen that about 10-20% of these nodules have been malignant in the examination of pathology (11) but this rate about FNA is uncertain and about 5-10% (3, 4). In various studies, FNA sensitivity has been reported in a wide range from 55% to 98% and its specificity was 70% to 100% (12-14). Also, the positive predictive value is reported 46-100% and its negative predictive value is 69-97% (15).

METHODS

Study design

The research procedure was accepted by the ethical committee (IR.SBMU.MSP.REC.1400.218) of the Shahid Beheshti University of Medical Sciences. This diagnostic study was performed on patients with thyroid nodules who referred to Loghman Hakim hospital (Tehran - Iran). Using the patient database, the data of patients with thyroid nodules who needed diagnostic FNA based on the findings of clinical examination and physician diagnosis (sonography and TSH) were evaluated. The data of 350 patients with FNA and cytology results after thyroid surgery were studied and the relevant findings based on the checklist were extracted from the files. A checklist was made for data extraction that was included age, sex, malignancy or not, type of pathological lesion based on FNA and histopathology after surgery, number of nodes, node size, and underlying disease.

Inclusion criteria were patients aged more than 20 years and lower than 70 years, presence of thyroid nodules who were nominated for FNA according to ultrasound, and were a candidate for surgery according to nodule size or FNA report. Exclusion criteria were patients who did not have an FNA report, lack of FNA report in patient's file, surgical contraindication, patients with incomplete data, and a lack of samples of patient pathology in the hospital archives. Pathological tissue samples were extracted from the pathology archive of the hospital and all samples were confirmed by an expert pathologist. The patients' FNA findings were compared with the pathology findings of postoperative samples. Age, sex, the occurrence of malignancy, type of pathological lesion based on FNA and histopathology after surgery, number of nodes, node size, underlying disease were extracted. Histopathological findings were evaluated based on thyroid imaging reporting and data system (TIRADS) (8).

All data were entered into SPSS version 24.0 software. Sensitivity, specificity, positive and negative predictive values were calculated by statistical analysis.

Sample size

According to 93%, sensitivity and 73% specificity for FNA in the study of Juan Li and Wang (16) and by choosing the 95% confidence level, 5% prevalence, and 8.5% error, 350 samples were determined for this study.

Statistical analysis

Frequency and percentage were used to describe the data. After proving the normality of the distribution of the studied variables by Kolmogorov- Smirnov test, Chi- square test or Fisher's exact test was used to examine the relationship between qualitative variables between groups.

All analyzes were performed by SPSS version 24.0 statistical software and a P-value less than 0.05 was considered statistically significant.

RESULTS

In this study, 359 patients were evaluated. Demographic information of 359 patients with thyroid nodules aged 20-70 years is examined in Table 1. Of the total number of patients, 279 patients (77.7%) were female and 80 (22.3%) were male. The mean age of all patients was 43.28 ± 13.37 years with a range of 10 to 87 years. The mean age and sexual frequency were evaluated separately for histopathological results after surgery. The mean age of patients in the group with benign thyroid nodules was significantly higher than patients with malignant thyroid nodules (P-value = 0.001) (Table 1).

Table 1. Demographic information of patients by surgical histopathology results

			Surgery Pathology		
		Total	Non- malignant, N = 228	Malignant, N = 131	P-value
Gender	Female	279 (77.7%)	180 (78.9%)	99 (75.6%)	0.511
	Male	80 (22.3%)	48 (21.1%)	32 (24.4%)	
Age (year)	Mean ± SD	43.28 ± 13.37	45.14 ± 12.48	40.12 ± 14.26	0.001

In terms of local symptoms, we found that 20 patients (16%) had hoarseness, 11 (8.8%) had dysphagia, 5 (4%) had dysphonia and 89 (71.2%) had dyspnea. There was a statistically significant difference between benign and malignant patients about local symptoms (P-value = 0.002). The frequency of different TIRADS classes between the two groups was statistically significant (P-value < 0.001). The highest frequency was related to category V with 112 (31.7%). These data are seen in Table 2.

Table 2. Clinical information of patients by results of surgical histopathology

			Surgery Pathology		
		Total	Non- malignant, N = 228	Malignant, N = 131	P-value**
Local symptoms	hoarseness	20 (16.0%)	11 (12.5%)	9 (24.3%)	0.002
	dysphagia	11 (8.8%)	3 (3.4%)	8 (21.6%)	
	dysphonia	5 (4.0%)	4 (4.5%)	1 (2.7%)	
	dyspnea	89 (71.2%)	70 (79.5%)	19 (51.4%)	
System symptoms	Symptoms of hypothyroidism	84 (79.2%)	54 (76.1%)	30 (85.7%)	0.312*
	Symptoms of hyperthyroidism	22 (20.8%)	17 (23.9%)	5 (14.3%)	
History of head and neck irradiation	yes	5 (1.5%)	2 (0.9%)	3 (2.4%)	0.362*
	no	330 (98.5%)	210 (99.1%)	120 (97.6%)	
Family history of MEN MTC and PTC	yes	40 (11.9%)	25 (11.7%)	15 (12.2%)	> 0.999*
	no	296 (88.1%)	188 (88.3%)	108 (87.8%)	
TSH level (mIU/L)	normal	260 (74.9%)	164 (72.9%)	96 (78.7%)	0.172
	high	30 (8.6%)	18 (8.0%)	12 (9.8%)	
	low	57 (16.4%)	43 (19.1%)	14 (11.5%)	
Location of the thyroid nodule	Right lobe	111 (33.4%)	67 (32.2%)	44 (35.5%)	0.106
	Left Lobe	184 (55.4%)	112 (53.8%)	72 (58.1%)	
	- Isthmus	37 (11.1%)	29 (13.9%)	8 (6.5%)	
TIRADS	I	4 (1.1%)	3 (1.3%)	1 (0.8%)	< 0.001
	II	78 (22.1%)	63 (28.0%)	15 (11.7%)	
	III	71 (20.1%)	62 (27.6%)	9 (7.0%)	
	Iva	35 (9.9%)	29 (12.9%)	6 (4.7%)	
	Ivb	48 (13.6%)	27 (12.0%)	21 (16.4%)	
	Ivc	5 (1.4%)	2 (0.9%)	3 (2.3%)	
	V	112 (31.7%)	39 (17.3%)	73 (57.0%)	
Focallity	Unifocal	78 (61.4%)	4 (80.0%)	74 (60.7%)	0.648
	Multifocal	49 (38.6%)	1 (20.0%)	48 (39.3%)	
Tumor necrosis	yes	6 (4.8%)	0 (0.0%)	6 (5.0%)	> 0.999
	no	120 (95.2%)	5 (100.0%)	115 (95.0%)	

****P-value based on Chi - square** ***P-value based on Fisher Exact test**

In Table 3, we assessed the FNA results in all patients with different histopathology results based on different types of pathological classification. Of 359 patients, 228 patients had benign nodules and 131 had malignant nodules in

postoperative histopathology. On the other hand, we examined the FNA results. One hundred seventy- five patients (49.2%) in this test had benign results, 35 (9.8%) Atypia of undetermined significance or follicular lesion of undetermined significance, 10 (2.8%) Follicular neoplasm or suspicious for a follicular neoplasm / Specify if Hurthle cell (oncocytic type), 80 (22.5%) were suspicious for malignancy and finally, 47 (132.2%) were malignant.

Table 3. Evaluation of FNA result in all patients and by histopathology results

Surgery Pathology	FNA	N (%)
Non malignant	Non- diagnostic or Unsatisfactory	7 (3.1%)
	Benign	152 (67.3%)
	Atypia of undetermined significance or follicular lesion of undetermined significance	29 (12.8%)
	Follicular neoplasm or suspicious for a follicular neoplasm/ Specify if Hurthle cell (oncocytic) type	7 (3.1%)
	Suspicious for malignancy	27 (11.9%)
	Malignant	4 (1.8%)
Malignant	Non- diagnostic or Unsatisfactory	2 (1.5%)
	Benign	23 (17.7%)
	Atypia of undetermined significance or follicular lesion of undetermined significance	6 (4.6%)
	Follicular neoplasm or suspicious for a follicular neoplasm/ Specify if Hurthle cell (oncocytic) type	3 (2.3%)
	Suspicious for malignancy	53 (40.8%)
	Malignant	43 (33.1%)
Total	Non- diagnostic or Unsatisfactory	9 (2.5%)
	Benign	175 (49.2%)
	Atypia of undetermined significance or follicular lesion of undetermined significance	35 (9.8%)
	Follicular neoplasm or suspicious for a follicular neoplasm/ Specify if Hurthle cell (oncocytic) type	10 (2.8%)
	Suspicious for malignancy	80 (22.5%)
	Malignant	47 (13.2%)

Of 228 benign patients as a result of the histopathological test, 7 nodules (3.1%) were Non - diagnostic or unsatisfactory, 152 (67.3%) Benign, 29 (12.8%) Atypia of undetermined significance or follicular lesion of undetermined significance, 7 (3.1 27) Follicular neoplasm or suspicious for a follicular neoplasm / Specify if Hurthle cell (oncocytic) type, 27 (119%) Suspicious for malignancy and 4 (1.8%) Malignant were in the FNA results. The FNA results in patients with malignant histopathology equal to 2 (1.5%), 23 (17.7%), 6 (4.6%), 3 (2.3%), 53 (40.8%), 43 (33.1%) and finally9 (2.5%), respectively based on above classification.

In other words, the FNA test correctly identified 152 out of 228 non - malignant patients and 43 patients out of 131 malignant patients.

Then, to calculate the sensitivity, specificity, positive predictive value, and negative predictive value of FNA in thyroid nodules, we converted histopathologic classification into two variables including non-malignant and malignant, in other words, patients with malignant and suspicious to malignant diagnosis were in the malignant group and the rest were in the non-malignant group. As shown in Table 4, the FNA correctly identified 195 benign patients and 96 malignant patients, which is a statistically significant difference (P-value < 0.001).

Table 4. Evaluation of FNA test performance

		Surgery Pathology		
		Malignant	non malignant	P-value
FNA	Malignant	96 (73.8%)	31 (13.7%)	< 0.001
	non malignant	34 (26.2%)	195 (86.3%)	

P-value based on Chi - square

Based on the results of Table 5, we found that the diagnostic method of FNA is acceptable in the diagnosis of benign and malignant patients with thyroid nodules.

As shown in this table, the sensitivity is equal to 74%, the specificity is equal to 86%, the positive predictive value is 76% and finally, the negative predictive value is equal to 85%.

Table 5. Sensitivity, specificity, positive predictive value and negative predictive value in thyroid nodules

Statistic	Value	95% CI
Sensitivity	73.85%	65.42% to 81.16%
Specificity	86.28%	81.10% to 90.49%
Positive Predictive Value (*)	75.59%	68.73% to 81.35%
Negative Predictive Value (*)	85.15%	81.05% to 88.49%
Accuracy (*)	81.74%	77.33% to 85.62%

The sensitivity indicates the test's ability to correctly diagnose malignancies. In other words, it shows the percentage of malignancies in patients who have correct malignancies. Specificity is the ability of the test to detect the benignity of nodules that are not malignant, in other words, the proportion of benign nodules that have FNA benign results. FNA test has 74% power to diagnose malignant patients and 86% power to diagnose benign patients.

The positive predictive value indicates the percentage of malignant patients in those whose test results were malignant. A negative predictive value indicates the percentage of benign patients in individuals whose test results were benign.

The accuracy of FNA in the present study is equal to 82%.

Results of sensitivity, specificity, positive predictive value, and negative predictive value are seen in table 5.

The ROC curve is used to compare the FNA test and postoperative histopathology. If the area under the curve is close to one, it indicates that the two tests are compatible.

The area under the curve is equal to 0.801 with an error Deviation of 0.026 and P-value is less than 0.001, which indicates the significance and relatively equal performance of the two tests.

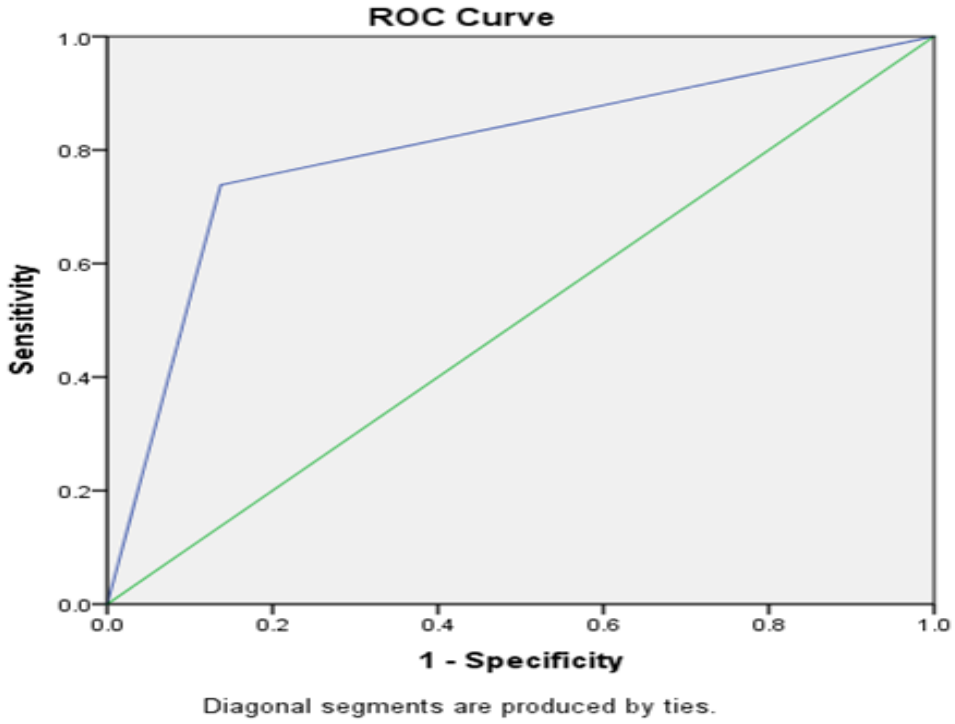

FIGURE 1. ROC Curve

Table 6. The area under the ROC curve

Area Under the Curve				
Test Result Variable (s): FNA				
Area	SE	P-value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.801	0.026	< 0.001	0.749	0.852

DISCUSSION

The present study aimed to evaluate the accuracy of FNA in comparison with postoperative histopathological findings in differentiating malignant from non-malignant thyroid nodules. In the study, 359 patients with thyroid nodules were evaluated, of which 77.7% were female and 22.3% were male. The mean age of all patients was 43.28 ± 13.37 years. It was found that the mean age of patients in the group with benign thyroid nodules was significantly higher than patients with malignant thyroid nodules. In fact, benign thyroid nodules were associated with older ages, and malignant nodules were associated with younger ages. A study by Orosco et al found that young patients had a higher risk of advanced thyroid cancer. This finding is similar to our finding. Orosco et al study also found that the female gender had a protective effect on malignant thyroid cancer. This finding was different from our finding of gender effect because in the present study it was found that the female gender was not associated with malignant or benign thyroid nodules. in the study of Orosco et al., It was found that most of the patients were in stage 1 based on TIRADS scoring (76%), but in the current study, it was found that most of the patients were in stage 5 based on TIRADS scoring, which in this respect they were different from each other (17).

In the study by Alolayan et al, it was found that the overall sensitivity of FNA was 91.2%, while its specificity was 71.65%. In the present study, it was found that the sensitivity was equal to 74%, the specificity was equal to 86%. These findings are very different from the study of Alolayan et al. This difference may come from the difference in the sample size of the two studies because the current study was performed on 359 participants but the Alolayan et al study was performed on 154 participants. One of the comparable features of these two studies is the geographical proximity of the two studies because both studies were conducted in the Middle East region, which in terms of nutrition and environmental conditions, both populations are in the same region. Then, this difference needs to be investigated in future studies (18). In the study of Narayanakar and Govinda Shetty, it was found that the sensitivity and specificity of FNA were 87.5% and 98%, respectively (19). The findings of this study are different from the current study. One of the advantages of the present study is the high sample size in the present study. The study population in the study of Narayanakar and Govinda Shetty was 60 people.

In a study conducted by Bozbıyık et al that was performed on a cytology sample of 127 during 6 years, sensitivity was 55.5%, specificity was 85%, and positive predictive value was 22.0% for FNA. Out of 127 cytology samples, 82 cases were benign (64.5%), 20 cases were suspicious to malignant (15.74%), 3 cases were malignant (2.36%) and 22 cases had insufficient samples (17.3%). In the present study, it was found that FNA sensitivity is 74%, specificity 86%, positive predictive value 76%, and negative predictive value 85%. The findings of our study were significantly different from the study of Bozbıyık et al except specificity that was similar in the both studies. As can be seen, in the present study the sensitivity of FNA was higher than the Bozbıyık et al study. Our findings had a higher percentage of positive predictive value, sensitivity, and PPV. The current study had a higher statistical population than the study of Bozbıyık et al and it is the advantage of this study compared to Bozbıyık et al study. In the present study, it was found that 63.5% of patients had benign pathology results and 36.5% had malignant results in histopathology, which in this regard, the two studies were almost similar (20).

In a study by Kaliszewski et al that was conducted to evaluate the accuracy of FNA in diagnosis of thyroid cancer, 1645 patients were assessed and 1479 patients had benign nodules and 166 patients had malignant nodules (10%). The sensitivity, specificity, PPV, NPV, and accuracy were 66%, 100%, 100%, 66%, and 97% in all cases. These rates were higher when the nodule was solitary. In the current study, we found that these rates were 74%, 86%, 76%, 85%, and 82% respectively. These differences may come from the difference in understudy population between the two studies. In the present study, all patients with both type of thyroid nodule including benign and malignant were assessed but in the Kaliszewski et al study, patients with thyroid cancer were evaluated. In fact, Kaliszewski et al evaluated patients with malignant nodules. Based on the two studies, it can be said, FNA has a higher accuracy in diagnosis of malignant tumor because in Kaliszewski et al study with assessment of malignant tumor, this parameter had higher rate than the present study (21).

In a study by Ucler et al that was performed to evaluate the accuracy of FNA in nodules larger than 3 centimeters, it was found that the accuracy rate was 80%, but when the nodule size was lower than 3 cm, the accuracy rate was equal to 60%. This comparison did not perform in our study but we observed that the accuracy rate was similar to Ucler et al study, when the nodule size was 3cm or larger (22). In a similar study with Ucler et al study that was performed by Yoon et al with similar population and method, it was found that the sensitivity was 96.7%, specificity was 85.9%, positive predictive value was 76.6%, negative predictive value was 98.2%, and accuracy was 89.4%. The accuracy was a little higher in the Yoon et al study that Ucler et al study. Other parameters were similar to the present study except sensitivity. The sensitivity rate was lower in our study. The reason of this lower rate may be come from higher population of our study. Our study was performed on 359 patient's data but Yoon et al evaluated 206 patient's data (23). It seems that in nodules greater than 3cm, the

accuracy rate of FNA for diagnosis of malignant tumor is more than 80% and it shows that FNA is a reliable test for deferring between malignant nodules and benign nodules.

In our study, we found that there was no association between a history of radiation to the head and neck and the incidence of malignancy. This finding may be caused by the fact that the prevalence of head and neck radiation is much lower now than in the past because in the past, one of the treatments for head lice was radiation to the head, which was effective in the development of thyroid cancer, but now this treatment does not perform.

CONCLUSION

The findings of this study suggest that age is associated with the development of malignancy and younger age is associated with the greater chance of thyroid malignancy. There is no association between gender and thyroid nodule malignancy. The degree of TIRADS is associated with a malignant or benign thyroid nodule and stave V is associated with the incidence of thyroid nodule malignancy. No association was found between tumor necrosis, focality, involved lobe, TSH level, family history of MEN, MTC, and PTC, history of head and neck radiation with malignancy. FNA sensitivity is 74%, specificity is 86%, the positive predictive value is 76%, and finally, the negative predictive value is 85%, and its accuracy for distinguishing malignant from the benign mass is 82%. According to the ROC curve, the compatibility of FNA with histopathological findings after thyroid surgery was 0.801, which is a sign of the high compatibility of FNA with the post-operation pathological assessment method as the most accurate method. It is suggested that in the future, studies will perform with larger statistical sample size and study of different populations in different parts of the world. The findings of this study indicated that FNA could be used with ease to diagnose thyroid nodules due to its high accuracy.

LIMITATIONS OF THE STUDY

Of the limitations of this study was incomplete data of patient's files and patients who had incomplete data were excluded

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Not declared.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTION

AE, TY, HR, AA, MHSS, SAF, NE, FA and SK were the principal investigators of the study. AE and TY revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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