COMPARISON OF ULTRASOUND FINDINGS WITH CYTOLOGIC RESULTS IN THYROID NODULES

E. Razmpa[1], H. Ghanaati[2], B. Naghibzadeh[3], P. Mazloom[1] and A. Kashfi[1]

1) Department of Otolaryngology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
2) Department of Radiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
3) Department of Otolaryngology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract- ***The nodular thyroid disease is one of the most common disturbances of the thyroid gland whereas malignant tumors are among the most unusual entities of it. Not only differentiation of these two spectra but also the problems to achieve early diagnosis and treatment, have been a matter of concern, research, and controversy. Two hundred patients were assessed at the Cancer Institute of Imam Khomeini Hospital as a retrospective research, considering the aim of evaluating and comparing the results of ultrasound and fine needle aspiration cytology with the postoperative histopathologic report. The ultrasound findings included location, number, size, feature, echogenicity, and presence of calcification; and those of the fine needle aspiration cytology consisted of benign, malignant, and suspicious samples. The cases mentioned as recurrent cancer or metastases of previous thyroid cancer were omitted from the study. In this research we found a sensitivity, specificity, accuracy of 92.3%, 76.4% and 88.1%, respectively, for fine needle aspiration cytology and also showed that the sensitivity and accuracy of fine needle aspiration cytology in diagnosis of malignant lesions of solid nodules was more than in cystic or mixed nodules of thyroid. Moreover, the incidence of false negatives in malignant cases of the studied sample was 7.7% (11/143). This rate was very higher in mixed and cystic lesions compared to benign ones (20% versus 5.7%). According to ultrasound findings, we showed that micro-calcification had a significant higher frequency in malignant nodules in comparison with the benign ones (4% in benign lesions versus 35% in malignant ones). The rate of malignancy in solid lesions revealed a significant increment compared to cystic and mixed nodules (p<0.0001). Moreover, the potential for malignancy in nodules with low echogenicity was very higher than high echogenicity producing nodules.***
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Correspondence:
E. Razmpa, Department of Otolaryngology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 8724578
Fax: +98 21 8729422
E-mail: erazmpa@tums.ac.ir

INTRODUCTION

Thyroid nodules are among common diseases of the thyroid gland especially in females. The incidence of thyroid nodules in the US is 4% among adults, the female to male ratio equals 4: 1. Contrary to thyroid nodules, the thyroid cancer is very rare and according to the Third Global Cancer Research, it has a 0.004% of annual prevalence (1). In recent years, fine needle aspiration cytology (FNAC) biopsy has been the greatest achievement in assessing thyroid nodules. In 1952, Soderstran established the FNAC biopsy and introduced it as a safe, simple, reliable, and tolerable method for the patients. It should be noted that insufficient sample for FNAC may result in making lots of errors in reporting the results, therefore, it explains high rate of false negative and even false positive results. Sensitivity of FNAC is over 90% and specificity of FNAC reaches almost 75%. The false positive and negative results of FNAC are reported to be almost 5%. One of the diagnostic problems is follicular neoplasm, followed by the cysts. It is better to take the sample of cysts from their walls or their residues after aspirating them, and it should be done with a large-bore needle. Also it has been demonstrated that if FNAC is performed under ultrasonography guide, lower false negative results would be achieved, as in one study almost 60% of undiagnosed cases of FNAC with palpation, were detected using FNAC under ultrasonographic guidance (2). Thyroid ultrasonography is one of the aids in diagnosing thyroid diseases. Ultrasound is an inexpensive method, without applying radiations and not producing tissue injury. It does not take much time and obviates the need for radio-opaque. In a study performed in an adult population using a 13 MHz transducer, one or more thyroid nodules were discovered in 34% of the cases (3). This figure is higher than in epidemiological studies, which estimates the frequency of thyroid nodules almost only 5% (4,5). It has found one or more nodules in only 21%, whereas Miki et al discovered a thyroid nodule in less than 21% (physical examination was positive in less than 2%) (3). In this article, our purpose is to determine the ability of ultrasonography in distinguishing malignant nodules of thyroid.

MATERIALS AND METHODS

This research was performed in a cross sectional, retrospective manner, evaluating 200 patients referred to the Cancer Institute of Imam Khomeini Hospital from 1995 to 1999. All data were obtained from the patients' records. The cancer relapses or metastases of thyroid neoplasm were omitted from the study. Ultrasonography was performed with Aloka 650 machine. The probe was 7.5 MHz (linear type). According to ultrasonographic and isotope scan findings, the largest cold nodule was selected for FNA in patients with more than one nodule. All patients underwent thyroid laboratory work up before FNA and approximately all cases showed euthyroid status with one or more cold nodules. Common variables included patients' age and sex. Ultrasound variables included location, size and number, echogenicity of a nodule in regard to the peripheral tissue, and the presence or absence of micro-calcification by considering the distal shadow. A benign etiology was suggested with a hyperechoic or extensively cystic nodule (over two thirds of the nodules), presence of a complete halo, multiple lesions, absence of hypervascularity, or absence of lateral cervical lymphadenopathy. Features proposing a malignant process include a solitary hypoechoic nodule, micro-calcification, ill-defined margins, incomplete halo, cervical lymphadenopathy, and central hypervascularity. Cytological variables consisted of inadequate, malignant, benign, and suspicious cases. Finding ground-glass nuclei of the cells was nearly confirmative for malignancy. Cytological atypia and presence of giant cells were suggestive for malignancy. In each case, the ultrasound and FNAC findings were compared with a gold standard diagnostic method (pathology) and the results were evaluated with the chi- square statistical test.

RESULTS

The incidence of malignancy in the patients was 72.5% (145/200). Among the malignant lesions, the most common was papillary carcinoma (48%), followed by follicular carcinoma (11.5%), medullary carcinoma (7.5%), anaplastic carcinoma (2.5%), Hürthle cell carcinoma (1.5%), and finally lymphoma, squamous cell carcinoma, and metastatic cancer had affected only one case. Among benign lesions, the nodular goiter and adenomatous goiter were more common than the other benign lesions. The average age of the patients with malignant nodules was 47±15.6 years, which was significantly higher than the average age of patients with benign nodules (38.2±14.1). Of course, this difference was not significant in patients under 25 years old. According to ultrasonographic findings, most of the diagnosable thyroid nodules were in the right lobe, followed by left lobe and thyroid isthmus. Most of the studied nodules were solitary (15 of 200 nodules, 75.5%). The frequency of malignancy was significantly higher in solitary nodules compared to multiple ones (Table 1). Micro-calcification was observed in only two of the 55 patients with benign modules (4%) versus 51 nodules of 145 malignant ones (35%, $p<0.05$, Table 2).

Table 1. Pathologic findings related to number of nodules (solitary or multiple).

Pathological Dx	**Solitary** **n (%)**	**Multiple** **n (%)**	**Total**
Benign Lesions	31 (56)	24 (44)	55
Malignant lesions	120 (83)	25 (17)	145
Papillary Ca	82 (85)	14 (15)	96
Follicular Ca	18 (78)	5 (22)	23
Medullary Ca	12 (80)	3 (20)	15
Anaplastic Ca	4 (80)	1 (20)	5
Hürthle Cell Ca	3 (100)	---	3
Lymphoma	---	1	1
Metastatic Ca	---	1	1
SCC	1	---	1
Total	151 (75.5)	49 (24.5)	200 (100)

Difference between malignant and benign lesions was significant by chi-square test ($P<0.001$)

Table 2. Relationship between ultrasonographic findings and final pathologic diagnosis

Pathological Dx	Nodule Feature (US)*				Echo-density*		
	Solid n (%)	Cystic n (%)	Mixed n (%)	Microcalcification* n (%)	Low n (%)	Moderate n (%)	Total
Benign lesions	23 (42)	8 (14)	24 (44)	2 (4)	12 (22)	43 (78)	55 (100)
Malignant lesions	124 (85)	0	21 (15.0)	51 (35)	110 (76)	35 (24)	145 (100)
Papillary Ca.	78 (81)	0	18 (19)	38 (40)	82 (85)	14 (15)	96 (66)
Follicular Ca.	20 (87)	0	3 (13)	3 (13)	7 (30)	16 (70)	23 (16)
Medullary Ca.	15 (100)	0	0	7 (47)	13 (87)	2 (13)	15 (10)
Hürthle Cell Ca.	3 (100)	0	0	0	1 (33)	2 (67)	3 (2)
Anaplastic Ca.	5 (100)	0	0	1 (20)	4 (80)	1 (20)	5 (3.5)
Lymphoma	1	0	0	1 (100)	1 (100)	0	1 (0.7)
SCC	1	0	0	0	1 (100)	0	1 (0.7)
Metastatic Ca.	1	0	0	1 (100)	1 (100)	0	1 (0.7)
total	147 (73.5)	8 (4)	45 (22.5)	53 (26.5)	122 (61)	78 (39)	200 (100)

* Differences between benign and Malignant Lesions by chi-square test were significant (P <0.05)

Table 3. Comparison of benign and malignant lesions in thyroid nodules

Parameter	Benign	Malignant	p
Total No:	55		
Mean Age	38.2±14.1	47.9±15.6	<0.001
Nodule diameter (cm)	2.48±1.42	2.61±1.42	=0.6103
Sex:			
Female	38 (29%)	92 (71%)	
Male	17 (24%)	53 (76%)	>0.05
Nodule Feature (US):			
Solid	23 (42%)	124 (85.5%)	
Cystic and Mixed	32 (58%)	21 (14.5%)	<0.0001
Nodule No:			
Solitary	31 (56%)	120 (83%)	<0.001
Multiple	24 (44%)	25 (17%)	
Echo-density:			
Low	12 (22%)	110 (76%)	
Moderate	43 (78%)	35 (24%)	<0.0001
Micro-Calcification	2 (4%)	51 (35%)	<0.0001

Table 4. Cytological findings in different histopathologic diagnoses

Pathological Dx	FNAC				Total
	Inadequate	Benign	Suspicious	Malignant	
Benign Lesions	4 (67%)	39 (78%)	11 (15%)	1 (1.4%)	55
Malignant Lesions	2 (33%)	11 (22%)	60)85%)	72 (98%)	145
Papillary Ca.	1	8	41	46	96
Follicular Ca.	---	1	14	8	23
Medullary Ca.	---	2	2	11	15
Hürthle Ca.	1	---	2	---	3
Anaplastic Ca	---	---	---	5	5
Lymphoma	---	---	---	1	1
SCC	---	---	---	1	1
Metastatic Ca.	---	---	---	1	1
total	6 (100%)	50 (100%)	71 (100%)	73 (100%)	200

Table 5. Statistical parameters of FNAC in diagnosis of malignant lesions of thyroid nodules

Parameter	Result
Adequate Cytology	194/200 (97%)
False Negative Incidence of Cancer	
All lesions (Solid and Cystic)	11/143 (7.7%)
Solid Nodules	7/123 (5.7%)
Cystic and Mixed	4/20 (20%)
Diagnostic Accuracy	
All Lesions	171/194 (88.1%)
Solid Nodules	128/144 (88.3%)
Cystic and Mixed	43/50 (86.0%)
Specificity	
All Lesions	39/51 (76.4%)
Solid Nodules	12/21 (57.1%)
Cystic and Mixed	27/30 (90%)
Sensitivity	
All lesions	132/143 (92.3%)
Solid Nodules	116/123 (94.3%)
Cystic and Mixed	16/20 (80.0%)
Positive Predictive Value	132/144 (91.6%)
Negative Predictive Value	39/50 (78%)

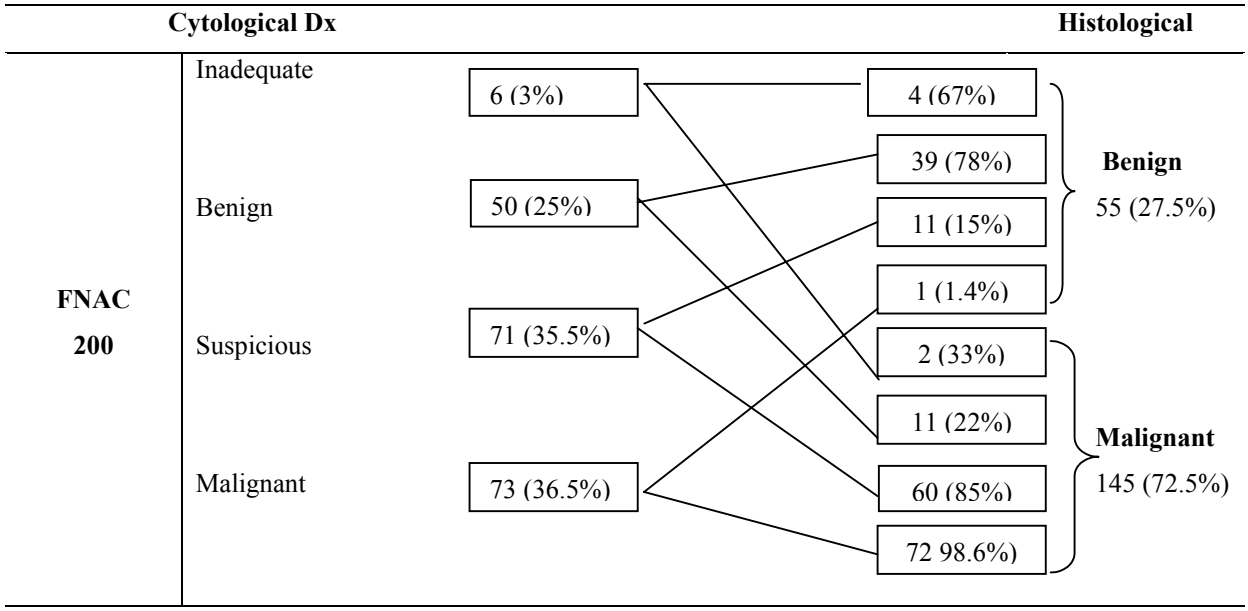

Fig 1. Assessment of relationship between cytological and histological findings

DISCUSSION

Ultrasonography can demonstrate the location, size, number, echo-texture and margins of thyroid nodules. High quality transducers could improve analysis of nodules contours and can demonstrate partial abnormalities, suggesting a neoplastic process. The incidence of malignancy was 72.5% in our study, which is higher than similar researches. Since this research is performed on the patients of a referal center devoted for evaluating malignancies, with regard to the type sample selection, it is impossible to judge about the incidence of malignancy in the considered samples or generalize it to other similar

researches. Carcinoma in malignant nodules is almost similar to other similar researches (4,5). In our research, the incidence of malignancy in men was 76% and in women was 71%, but comparing to other studies this difference was not significant. Perhaps mean age of patients with malignant nodules was significantly higher than those with benign ones (Table 3) (4-6). The incidence of malignancy in FNAC findings was very high for follicular neoplasm though it has been mentioned that only 15% of FNAC suspected lesions are malignant at the end (1). However, this rate was 85% in our study, which probably was because of the method of selecting the patients, as mentioned before. Moreover, according to table 4, it was shown that the rate of suspicious cases of malignant lesions was more in follicular carcinoma compared with other lesions. This finding is perfectly similar to the other reports showing the lower ability of FNAC in diagnosing such cases (7,8). Considering other matters of sensitivity, accuracy and false negativity of FNAC among solid, cystic, and mixed lesions, the results were perfectly alike resembling statistical research (Table 5) (1,4-6). Evaluating the ultrasound findings, according to table 2, most of the cystic and mixed lesions (in ultrasonography) were finally benign, this finding had been confirmed in similar studies (9,10). Also, we showed that the presence of micro-calcification in ultrasonography of thyroid nodules is strongly related to malignancy. Similarly, malignant nodules probably are more hypodense in ultrasonography, compared to benign nodules. Even though most of researchers and physicians believe that FNAC especially before operation, is the best method for diagnosis and follow-up of thyroid nodules, we could never ignore the limitations of this approach. Moreover, FNAC is limited in interpreting cystic, small and occult nodules of thyroid and follicular carcinoma of the gland (5,9-11). Therefore, it is necessary to use other methods such as thyroid scan, ultrasonography, and hormone suppression therapy for determining the indication of surgery and follow-up of thyroid nodules. Although the role of sonography in screening and follow-up of thyroid nodules is of low importance according to some studies (12), we have also had several studies indicating its significance and role in thyroid nodules. In a research on 311 benign nodules of the thyroid gland, performed by Merceron et al, they showed that ultrasound together with FNAC and physical examination had a significant role for the accurate follow-up of these patients. If malignant signs of ultrasound (nodule growth, cystic degeneration, and change of echogenicity) appear in periodic follow-up evaluations, necessary interventions such as FNAC or surgery should be performed (13). In a research by Solbiati et al on the FNAC supported follicular neoplasm, they showed that hypoechogenicity could be a strong criterion in precise diagnosis of a malignant nodule (14).

In 1994, Katagiri and co-workers performed a study on 120 thyroid nodules (64 were benign, 56 were malignant) in Japan (15). By using ultrasonographic criteria (the shape, borderline, internal echogenicity of the nodule, hypoechoic points, surface echogenicity of in and cystic appearance), it was shown that in differentiating malignant lesions, ultrasound had a sensitivity, specificity, and accuracy of 82%, 78%, and 80% respectively. It was interesting that these results by using FNAC did not show significant difference with ultrasound observance. In conclusion ultrasonography, a non-invasive inexpensive diagnostic tool, plays an important role in thyroid nodules. It has an acceptable sensitivity and specificity and could be an invaluable adjunct in pre- and postoperative settings to reduce the patients discomfort due to misdiagnosis. Finally, we showed that ultrasound was a useful approach in diagnosis and especially in follow-up of the patients with thyroid nodules and removes ambiguity.

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