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ORIGINAL ARTICLE

Ultrasonographic evaluation of thyroid nodules: comparison of ultrasonographic, cytological, and histopathological findings

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Abstract Thyroid ultrasonography (US) and fine needle aspiration biopsy (FNAB) are the most important tools in evaluating thyroid nodules. A total of 3,404 nodules in 2,082 cases referred to our clinic between 2005 and 2008 were analyzed retrospectively. Considering US features of nodules, risk factors predicting malignancy were: margin irregularity as the most important predictor, hypoechoic pattern and microcalcification (Odds ratios: 63.2, 13.3, 7.03, respectively). Cytologic results of the patients were as follows: 1,718 (82.5%) benign, 196 (9.4%) suspicious, 68 (3.3%) nondiagnostic, and 100 (4.8%) malignant. In histopathologic examination, we determined a malignancy rate of 7.59% (158/2082). We calculated the sensitivity of FNAB as 89.16%, specificity as 98.77%, positive predictive value as 96.10%, negative predictive value as 96.39%, and accuracy as 96.32%. In cytologic examination, the malignancy rate of subcentimetric ($\leq$1 cm) nodules was higher than supracentimetric (>1 cm) nodules (5.1% vs. 1.5%, $P = 0.001$). In postoperative histopathologic examination, although the malignancy rate of subcentimetric nodules was higher than that of supracentimetric nodules, the difference was statistically insignificant (5.5%, 4.4%, respectively; $P > 0.05$). Cytologically diagnosed malignancy was detected in 4.5% of patients with multiple nodules, while it was present in 6% of patients with solitary nodule indicating no significant difference. However, postoperative histopathologic examination revealed a significantly higher malignancy rate in patients with solitary nodule compared to in patients with multiple nodules (11.7%, 6.5%; respectively, $P < 0.001$). The malignancy rate of patients operated for suspicious cytology was found to be 46.15%; for nondiagnostic cytology, it was 64.29%. In

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conclusion, ultrasonographically, hypoechoic pattern, microcalcification and margin irregularity of thyroid nodules are important features in determining the malignancy risk. The nodule size alone still remains inadequate to exclude malignancy risk.

Keywords Ultrasonography · Fine needle aspiration biopsy · Cytology · Histopathology

Introduction

Nodular goiter is the most frequently detected disease of the thyroid gland. Generally, 4–7% of adult populations have a palpable thyroid nodule, but 19–67% of them have nodules that can be detected by ultrasonography (US). Of the palpable nodules, approximately 5% are diagnosed with malignancy [1]. A detailed history, physical examination, and serum thyrotropin measurement are the first steps for evaluating a patient with a thyroid nodule [2]. US is very useful in detecting thyroid nodules but is not very accurate in differentiating malignant lesions from benign lesions [3].

Recently, several studies have been performed using high-resolution US to determine features of a malignant thyroid nodule, such as hypoechogenicity, microcalcification, margin irregularity, increased blood flow in the nodule demonstrated by doppler, local invasion, or regional lymphadenopathy [3–9]. Fine needle aspiration biopsy (FNAB) has become the most cost-effective, efficient, noninvasive method for distinguishing between benign and malignant nodules. It is recommended for palpable nodules; however, the indication of this procedure for nonpalpable nodules is controversial [10].

In this study, we aimed to determine the predictive value of US features of nodules for malignancy and investigate the effects of factors like gender, age, nodule size and number on malignancy. In addition, we compared cytologic results of nodules with final histopathologic diagnoses.

Materials and methods

Patients

A total of 2,082 cases admitted to our clinic between 2005 and 2008 and 3,404 nodules in these patients were included in the study. There were 1,744 (83.8%) women and 338 (16.2%) men. The mean age was 48.22 ± 12.82 (15–89) years. Thyroid functions were normal in 1,369 (65.8%) patients, while 404 (19.4%) patients had hypothyroidism and 309 (14.7%) patients had hyperthyroidism. Results were analyzed retrospectively. Thyroid US and US guidance FNAB (USgFNAB) were performed by our experienced endocrinologists (KG, RE, BC).

Thyroid ultrasonography

Thyroid US was performed in all cases (Esaote Technos-MPX and 10 MHz probe; Geneva, Italy). Features of nodules were classified for: (1) echogenicity: as isoechoic, hypoechoic, hyperecoic, or anechoic; (2) echoic texture: as solid, mixed, or cystic (if the cystic component occupied an area of less than 25%, it was considered as solid; between 25 and 74% as mixed and 75 and 100% as cystic); (3) presence of microcalcification: as "present" or "absent"; (4) presence of macrocalcification: as "present" or "absent"; (5) presence of halo: as "present" or "absent"; and (6) regularity of nodule margin: as regular or irregular. In addition, thyroid parenchyma, number of nodules [solitary thyroid nodule (STN): 1 nodule, multiple thyroid nodules (MTN): ≥2 nodules; independent of nodule size], and their sizes (subcentimeter ≤1 cm or supracentimeter >1 cm) were evaluated by US.

Fine needle aspiration biopsy

Informed consent was taken from all cases after explanation of the FNAB procedure. FNAB was carried out with US guidance (Logic Pro 200 GE and 7.5 MHz probe; Kyunggigo, Korea). All nodules >1 cm and nodules ≤1 cm with at least one of the US findings anticipating malignancy such as hypoechoism, microcalcification, margin irregularity, and absence of halo were evaluated with FNAB. FNAB was carried out with 27 gauge needle and 20 ml syringe under US guidance using free hand technique. Aspiration was performed at least 4–6 times. Biopsy was taken a minimum of 2–4 times from each nodule. Samples were obtained from the solid component in nodules with mixed echoic texture. Biopsies were taken from the cystic nodules after an aspiration. Furthermore, the cystic content was examined pathologically after centrifugation and the material was extruded onto a slide for smear preparation. All aspiration samples were spread on slides and fixed by air-drying. They were stained with hematoxylin-eosin and Giemsa. Material was considered sufficient when minimally 6 groups consisting of at least 10 well-protected thyroid epithelial cells were present [11]. Cytologic diagnoses of FNAB were classified as benign, suspicious for malignancy, malignant, and nondiagnostic. Colloidal nodule, lymphocytic thyroiditis, nodular goiter, and nodular hyperplasia were accepted as benign cytology. Follicular lesion/neoplasm, Hürthle cell lesion/neoplasm, and lesion suspicious for papillary carcinoma were accepted as suspicious cytology. Papillary carcinoma, medullary

carcinoma, and anaplastic carcinoma were accepted as malignant cytology.

Histopathology

Patients with malignant or suspicious cytology results of FNAB underwent surgery. In nodules with nondiagnostic cytology, biopsies were repeated. If still nondiagnostic, surgery was performed for nodules that were clinically and ultrasonographically suspicious. Large goiter with or without symptoms of tracheal and/or esophageal compression were other indications for surgery. Four hundred eighty-three of 2,082 patients included in this study were operated in our hospital. After the routine tissue follow-up procedures, the samples were embedded in paraffin blocks. Sections obtained from these blocks were stained with hematoxylin-eosin and examined under a light microscope. Histopathologic results of operated patients were grouped as malignant (papillary carcinoma, follicular carcinoma, Hürthle cell carcinoma, anaplastic carcinoma, medullary carcinoma) or benign (nodular hyperplasia, colloidal goiter, lymphocytic thyroiditis, Hashimoto thyroiditis, follicular adenoma, Hürthle cell adenoma).

Statistical analysis

Statistical data were analyzed using the SPSS 11.5 (SPSS Inc.) software package. Continuous data were presented as mean ± standard deviation (SD). Nominal data were given as number of cases and (%). Mean ages were compared by Student's *t* test. Nominal data were evaluated by Pearson's chi-square test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for each qualification of nodule. A backward stepwise selected logistic regression analysis was performed to define the best predictors within nodule qualifications determining malignity. Odds ratio (OR), 95% confidence intervals (CIs), and level of significance were calculated for each independent variable. A "*P*" value less than 0.05 was considered statistically significant.

Results

We summarized the results in five sections.

Thyroid US findings

STN was present in 435 (20.9%) patients and MTN in 1,647 (79.1%) patients. Seven hundred twenty-four of 3,404 nodules were subcentimetric (21.3%) and 2,680 were supracentimetric (78.8%). Other US findings are shown in Table 1.

Ultrasonography-guided FNAB cytologic results

FNAB was performed on 3,404 nodules of 2,082 cases. After the first USgFNABs, the rate of nondiagnostic cytology was 9.3% and a second FNAB was repeated in this group. Cytology was reported as nondiagnostic again in 10.8% of these. Final cytologic result of these two USgFNABs was utilized in analysis. Accordingly, we determined that, of 3,404 nodules, 2,996 had benign (88%), 219 suspicious (6.4%), 77 nondiagnostic (2.3%), and 112 (3.3%) malignant cytological findings. Cytologically, a patient was accepted as malignant if there was more than one nodule with different cytologies in the same patient and one of them was malignant. The patient was accepted to have suspicious cytology if one of the nodules was suspicious, and as nondiagnostic if one of the nodules was nondiagnostic. With respect to this evaluation, 1,718 cases were benign (82.5%), 196 were suspicious (9.4%), 68 were nondiagnostic (3.3%), and 100 were malignant (4.8%). The mean age of patients with benign cytology was 48.46 ± 12.87 year and of malignant cases was 46.08 ± 12.90 year; the difference between them was statistically insignificant ($P = 0.073$; OR: 0.99; 95% CI: 0.97–1.0). The malignancy rate in women was 4.9% and in men was 4.1%, and the difference was also insignificant ($P = 0.051$). According to FNAB results, overall 219 nodules (196 patients) were accepted to have suspicious cytology, of which, 121 (105 cases) were suspicious for papillary carcinoma, 64 (59 cases) for Hürthle cell lesion/neoplasm, and 34 (32 cases) for follicular lesion/neoplasm.

Comparison of US features and cytologic results

When the US features of nodules with malignant and benign cytologic results were compared, we found that with respect to nodule size, 20.3% of benign nodules and 33% of malignant nodules were subcentimetric. The malignancy rate of subcentimetric nodules was 5.1% and of supracentimetric nodules was 1.5%, and the difference was statistically significant ($P = 0.001$). STN was present in 341 (19.8%) of the patients with benign cytology and in 26 (26.0%) with malignant cytology. Malignancy rates of STN and MTN were found to be 6 and 4.5%, respectively, and the difference was not statistically significant ($P = 0.136$) (OR: 1.42, 95% CIs: 0.9–2.26). Figure 1 shows percentage distribution of US features of nodules with malignant and benign cytologies.

After comparing US features of nodules with malignant and benign cytologies, diagnostic values of variables that are found to have statistically significance were calculated (Table 2). Generally, sensitivity of US features was high, but specificity and PPV were low. Margin irregularity had the highest specificity with 87.3% (OR: 63.21, 95% CIs:

Table 1 Ultrasonography findings and cytologic results of thyroid nodules on which fine needle aspiration biopsy was performed

Ultrasonography findings	Total	Cytological diagnosis				*P*
		Benign	Suspicious	Nondiagnostic	Malignant	
Total (nodule)	3404	2996 (88%)	219 (6.4%)	77(2.3%)	112 (3.3%)	
Total (patient)[a]	2082	1718 (82.5%)	196 (9.4%)	68 (3.3%)	100 (4.8%)	
Sex						0.051
Female	1744	1434 (82.2%)	165 (9.5%)	59 (3.4%)	86 (4.9%)	
Male	338	284 (84%)	31 (9.2%)	9 (2.7%)	14 (4.1%)	
Nodule number						0.136
Single nodule	435	341 (78.4%)	57 (13.1%)	11 (2.5%)	26 (6%)	
Multiple nodule	1647	1377 (83.6%)	139 (8.4%)	57 (3.5%)	74 (4.5%)	
Size						**<0.001**
Subcentimeter	724 (21.3%)	609 (84.1%)	42 (5.8%)	36 (5%)	37 (5.1%)	
Supracentimeter	2680 (78.7%)	2387 (89.1%)	177 (6.6%)	41 (1.5%)	75 (1.5%)	
Echogenicity						**<0.001**[b]
Isoechoic	2027 (59.5%)	1903 (93.9%)	79 (3.9%)	30 (1.5%)	15 (0.7%)	
Hypoechoic	1251 (36.8%)	980 (78.3%)	136 (10.9%)	38 (3%)	97 (7.8%)	
Anechoic	95 (2.8%)	87 (91.6%)	0 (0%)	8 (8.4%)	0 (0%)	
Hyperechoic	31 (0.9%)	26 (83.9%)	4 (12.9%)	1 (3.2%)	0 (0%)	
Microcalcification						**<0.001**
Present	1643 (48.3%)	1380 (84%)	130 (7.9%)	37 (2.3%)	96 (5.8%)	
Absent	1761 (51.7%)	1616 (91.8%)	89 (5.1%)	40 (2.3%)	16 (0.9%)	
Macrocalcification						0.054
Present	421 (12.4%)	370 (87.9%)	28 (6.7%)	7 (1.7%)	16 (3.8%)	
Absent	2983 (87.6)	2626 (88%)	191 (6.4%)	70 (2.3%)	96 (3.2%)	
Margins						**<0.001**
Regular	2794 (82.1%)	2616 (93.6%)	110 (3.9%)	57 (2%)	11 (0.4%)	
Irregular	610 (17.9%)	380 (62.3%)	109 (17.9%)	20 (3.3%)	101 (16.6%)	
Composition						**<0.001**[c]
Solid	3057 (89.8%)	2669 (87.3%)	214 (7%)	63 (2.1%)	111 (3.6%)	
Mixed	252 (7.4%)	239 (94.8%)	5 (2%)	7 (2.8%)	1 (0.4%)	
Cystic	95 (2.8%)	87 (91.6%)	0 (0%)	8 (8.4%)	0 (0%)	
Halo sign						**<0.001**
Absent	2399 (70.5%)	2078 (86.6%)	154 (6.4%)	57 (2.4%)	110 (4.6%)	
Present	1004 (29.5%)	917 (91.3%)	65 (6.5%)	20 (2.0%)	2 (0.2%)	

P value: difference between benign and malignant nodules

[a] According to patient number

[b] Hypoechoic compared with isoechoic + hyperechoic + anechoic

[c] Solid compared with mixed + cystic

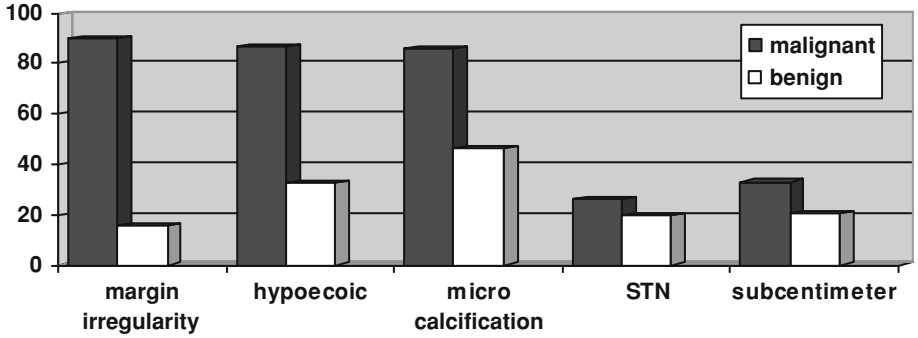

Fig. 1 Percentage distribution of US features of nodules with malignant and benign cytologies. (*STN* solitary thyroid nodule)

Table 2 Diagnostic value of ultrasonography findings for the detection of malignant thyroid nodules

	Hypoechoic	Solid composition	Microcalcification	Absent of halo sign	Margin irregularity
Sensitivity	97/112	111/112	96/112	110/112	101/112
	(86.6%)	(99.1%)	(85.7%)	(98.2%)	(90.2%)
Specificity	2016/2996	326/2996	1616/2996	917/2996	2616/2996
	(67.9%)	(10.9%)	(53.9%)	(30.6%)	(87.3%)
PPV	97/1077	111/2781	96/1476	110/2188	101/481
	(9.0%)	(4.0%)	(6.5%)	(5.0%)	(21.0%)
NPV	2016/2031	326/327	1616/1632	917/919	2616/2627
	(99.3%)	(99.7%)	(99.0%)	(99.8%)	(99.6%)
Accuracy	2113/3108	437/3108	1712/3108	1017/3108	2717/3108
	(68.0%)	(14.1%)	(55.1%)	(33.0%)	(87.4%)

Sensitivity: Number of true positives divided by the number of true positives plus the number of false negatives

Specificity: Number of true negatives divided by the number of true negatives plus the number of false positives

Positive predictive value (PPV): Number of true positives divided by the number of true positives plus the number of false positives

Negative predictive value (NPV): Number of true negatives divided by the number of true negatives plus the number of false negatives

Accuracy: Number of true positives plus the number of true negatives divided by the number of true positives plus the number of true negatives plus the number of false positives plus the number of false negatives

33.61–118.87), followed by hypoechogenicity with 67.9% (OR: 13.3, 95% CIs: 7.68–23.04). Furthermore, specificity of presence of microcalcification was 53.9% (OR: 7.03, 95% CIs: 4.12–11.99).

The presence of a single or two US features significant for diagnosis of malignancy and presence of combination of two or more together were compared with logistic regression analysis. The results are summarized in Table 3. When the coexistence of hypoechogenicity and margin irregularity and microcalcification was compared with the coexistence of one or two of these, sensitivity was detected as 65.2%, specificity as 98.7%, PPV as 71.6%, and NPV as 98.2%. Generally, while the sensitivity decreases when US features are found together, specificity and PPV increase.

Histopathologic results

Four hundred and eighty-three of 2,082 patients included in this study were operated in our hospital. Of the operated patients, preoperative FNAB results were benign in 249 patients, suspicious in 143, malignant in 77, and nondiagnostic in 14, cytologically. In postoperative histopathologic examination, thyroid cancer was detected in 158 cases and 325 cases were reported as benign. Consequently, the

Table 3 Diagnostic value of different combinations of significant ultrasonography findings in distinguishing between benign and malignant nodules

Ultrasonography findings	Benign ($n = 2996$)	Malignant ($n = 112$)	P	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
A–B			<0.001				
Both present (+)	331	82		73.9	83.7	19.9	98.3
One present (+)	1,698	29					
A–C			<0.001				
Both present (+)	94	86		76.8	92.6	47.8	97.8
One present (+)	1,172	26					
C–B			<0.001				
Both present (+)	128	87		79.1	92.2	40.5	98.5
One present (+)	1,504	23					
A–B–C			<0.001				
All three present(+)	29	73		65.2	98.7	71.6	98.2
Two present (+)	466	36					
One present (+)	1,721	3					

A Hypoechogenicity, *B* Microcalcifications, *C* Irregular margins, *n:* number of nodules

Table 4 Pathologic diagnoses in 143 cases with suspicious diagnosis cytologically

Cytological diagnosis	Surgical histopathology		Total
	Malignant	Benign	
Hürthle cell lesion/neoplasm	18 (40%)	27 (60%)	45 (31.47%)
Follicular lesion/neoplasm	9 (37.5%)	15 (62.5%)	24 (16.78%)
Suspicious for papillary carcinoma	39 (52.70%)	35 (47.3%)	74 (51.75%)
Total	66 (46.15%)	77 (53.85%)	143 (100%)

histopathologically confirmed malignancy rate was 7.59% (158/2082). Of the operated patients, 389 were women and 94 were men. One hundred and thirty-five of the histopathologically malignant cases were women and 23 were men. The histopathologically confirmed malignancy rate of women was 7.74% (135/1744) and of men was 6.8% (23/338). As to histopathologic results, mean age of malignant patients was 46.36 ± 11.94 year and of benign patients was 46.36 ± 11.94 year. Of the operated 483 patients, 130 had STN and 353 had MTN. In the postoperative histopathologic examination, 51 of the malignant cases had STN and 107 had MTN. Accordingly, histopathologically confirmed malignancy rate in STN was 11.7% (51/435) and in MTN was 6.5% (107/1647), and the difference between them was statistically significant ($P < 0.001$). Fifty-five of the patients with subcentimetric nodule underwent operation for cytologic results, while 248 of the patients with supracentimetric nodule were operated for cytology. After the operation, of the malignant cases, 40 were detected in the subcentimetric and 118 in the supracentimetric nodules. Histopathologically confirmed malignancy rate of subcentimetric nodules was 5.5% (40/724) and of supracentimetric nodules was 4.4% (118/2680) ($P = 0.2$). Of 158 patients in whom thyroid cancer was detected, 141 were papillary cancer (89.2%), 9 were follicular cancer (5.7%), 5 were Hürthle cell cancer (3.2%), and 3 were medullary cancer (1.9%).

Comparison of cytologic and histopathologic results

Considering FNAB results, in 9 (3.62%) of 249 patients operated with benign cytology, in 9 (64.29%) of 14 patients operated with nondiagnostic cytology, in 66 (46.15%) of 143 patients operated with suspicious cytology, and in 74 (96.10%) of 77 patients operated with malignant cytology, thyroid malignancy was detected in the postoperative histopathological examination. By excluding suspicious and nondiagnostic cytologies, when the postoperative results of nodules with malignant and benign FNAB results were compared, the sensitivity of FNAB was 89.16%, specificity 98.77%, PPV 96.10%, NPV 96.39%, and accuracy 96.32%.

Histopathologically confirmed malignancy rate in patients operated for Hürthle cell lesion/neoplasm in cytology was 40%. Malignancy rates in patients operated for follicular lesion/neoplasm and suspicious papillary cancer cytology were found to be 37.5 and 52.7%, respectively (Table 4).

Discussion

Evaluation of thyroid nodules by US has become widespread. The recently published guidelines for diagnosing patients with thyroid nodules recommended measurement of serum thyrotropin and US as the first line [12, 13]. Diagnostic accuracy of US in thyroid nodules has been considerably developed with more advanced US equipment like high-frequency US probes. These technical advances have enabled the researchers to report enhanced results in prediction of malignant thyroid nodules by US.

With this study, we were able to evaluate many variables alltogether (age, sex, US features of nodules, and nodule sizes) that may have predictive value to detect malignancy in thyroid nodules. Also, we examined correlation of cytologic and histopathologic results.

Several US features have been found to be associated with an increased risk of thyroid cancer. However, the sensitivities, specificities, NPV and PPV for these criteria vary widely from study to study, and no US feature has both a high sensitivity and high PPV for thyroid cancer. Most of the studies in the literature reported that microcalcifications were more common in histologically confirmed malignant lesions than in benign nodules [9, 14]. In the current study, most important US feature to predict malignancy was found to be margin irregularity (sensitivity 90.2%, specificity 87.3%, OR: 63.2) followed by hypoechoic pattern (OR: 13.3). Predictive value of microcalcification was lower (OR: 7.03). In concordance with our results, Papini et al. and Koike et al. had reported margin irregularity as a common finding of malignant thyroid nodules [4, 15]. Additionally, it was shown in different studies that hypoechoic texture was related with malignancy [5, 16, 17]. We assessed the diagnostic value of combination of two or more US findings to find out if this provides a better diagnostic accuracy in determining malignancy risk than only one of these findings. There are a limited number of studies examining importance of evaluating US features together. Rago et al. had combined conventional and color Doppler

US findings and found that absent halo sign and microcalcifications on US with marked intranodular blood flow was the most specific combination of the two techniques (specificity 97.2%, sensitivity 16.6%) [18]. We found hypoechogenicity and microcalcification and margin irregularity as the most predictive combination (sensitivity 65.2%, specificity 98.7%, PPV 71.6%). Consistent with our results, Asteria et al. [5] also reported hypoechogenicity, microcalcification and margin irregularity to be the most specific combination (sensitivity 41%, specificity 99%). Generally, in combinations of US findings, it is seen that specificity is increased while sensitivity is decreased.

In different studies, the malignancy rate of thyroid nodules according to FNAB is reported to be between 1 and 10% (average 3.5%) [19]. In the present study, it was 3.3% cytologically (4.8% per patients), and 7.6% histopathologically. Lin et al. [20] pronounced the malignancy rate cytologically as 3.4% and histopathologically as 3.95%. On the other hand, Kim et al. [8] established the malignancy rate to be as high as 20.8% (21.6% per patients), cytologically. Variations in malignancy rates may be due to differences in patient selection, procedure technique, nodule size, and FNAB indications. Gharib et al. established FNAB results from 7 series and reported an accuracy approaching 95%, sensitivity of 65 to 98% (mean: 83%), and a specificity of 72 to 100% (mean: 92%) [19]. In our study, sensitivity of FNAB was 89.16%, specificity 98.77%, PPV 96.10%, NPV 96.39%, and accuracy 96.32%.

Thyroid nodules are four-fold more frequent in women compared to men [21]. In the literature male gender and age less than 20 years and over 60 years are reported to be associated with a higher thyroid malignancy risk [22]. In our study, we found that age and sex were not associated with increased risk of malignancy in thyroid nodules. In some of recent studies [9, 17, 23], no relation between malignancy and age and sex was detected, even there are studies reporting higher malignancy rate in women compared to men [8]. Similar incidence of thyroid cancer in both sexes may be attributed to tendency to perform FNAB in subcentimetric nodules, more males admitting to hospital for routine control compared to past and genetic factors. Sundram et al. [24] reported a female preponderance of mortality of thyroid malignancies in Bangladesh, Laos, and Malaysia, whereas lower mortality in women was reported in China, Vietnam, and New Zealand.

There is considerable variation among published recommendations and guidelines for appropriate evaluation of patients with MTN. The American Thyroid Association guidelines recommend FNAB evaluation of nodules larger than 1–1.5 cm with suspicious sonographic appearance or of the largest nodule only if none has suspicious sonographic features [13]. The American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi recommendations (AACE/AME) for evaluating patients with MTN differ because they consider the US features the principal indication for evaluating nodules irrespective of their size [12]. We prefer to carry out FNAB for all nodules larger than 1 cm and for nodules smaller than 1 cm with suspicious US findings. Although, cytologically diagnosed malignancy was present in 4.5% of patients with MTN, it was present in 6% of patients with STN and the difference was not significant. However, postoperative histopathologic examination revealed a significantly higher malignancy rate in patients with STN compared to in patients with MTN (11.7%, 6.5%; respectively, $P < 0.001$). This difference possibly originates from higher number of patients operated for suspicious cytology in the STN group resulting with more malignancy detected in histopathologic examination. Kumar et al. [25] reported that the risk of thyroid cancer was lower in patients with MTN than in those with STN. Unlike our results, Cappelli et al. [9] reported the malignancy rate with histologic examination in MTN as 5.3% and in STN as 4.1%, and the difference was significant ($P = 0.022$). Frates et al. [26] found no difference in terms of malignancy between STN and MTN. Variations in nodule size and FNAB indications in different studies may have played role in these different malignancy rates. We think it would be more accurate to consider US findings instead of nodule number and size while performing FNAB in patients with MTN.

The detection rate of subcentimeter nodules has increased with the increasing use of high-resolution thyroid US [27]. However, the approach to subcentimeter nodules is still controversial. While some clinicians recommend US-gFNAB [3], others admit that clinical follow-up (palpation) is sufficient if there is no history of familial thyroid cancer or radiation to the head or neck [10]. We performed US-gFNAB in subcentimetric nodules in case of suspicious US features (hypoechoic, microcalcification, irregular margin, absence of halo). Cytologically, malignancy rate was higher in subcentimetric nodules compared to supracentimetric nodules (5.1 and 1.5%, respectively). We think the most important reason for this result was probably careful selection of the lesions to submit to FNAB in the patients with subcentimetric nodules. Considering the postoperative histopathologic examination, the malignancy rate was slightly higher in subcentimetric nodule and the difference was insignificant (5.5 and 4.4%, respectively). Increase in malignancy rate in supracentimetric nodules after histopathologic examination may be related to higher number of nodules with suspicious cytology and malignant histopathology in this group or to false negative cytology results in larger nodules. It was demonstrated in previous studies that there is no significant relation between nodule size and malignancy [3, 16, 17, 26]. Kim et al. [8] reported significantly higher malignancy rates in subcentimetric nodules

than in supracentimetric nodules ($P < 0.005$). Papini et al. [4] demonstrated cancer prevalence in subcentimetric and supracentimetric nodules as 9.1 and 7.0%, respectively. Our finding suggest that subcentimetric nodules have the same potential for malignancy as supracentimetric ones. We think nodule size alone is not a predictor for malignancy and US features are more important.

Fine needle aspiration biopsy has two major limitations: nondiagnostic results and suspicious results. The rate of nondiagnostic cytologic results varies from 2 to 21% [19]. Clinical approach in nondiagnostic thyroid nodules is a controversial issue. Prevalence of malignancy in nondiagnostic cytology was reported to be 9–37% [28, 29]. We found a higher malignancy rate (64.3%) in our series. The reason for this may be our preference of surgical management in patients with clinically and ultrasonographically (hypoechoic, microcalcific, irregular margins) suspicious nodules rather than in all patients with nondiagnostic cytology. Considering this result, nondiagnostic cytologies might not be of benign cytology and should be evaluated carefully. Our suggestion is to prefer surgical management if nondiagnostic cytology is clinically and ultrasonographically suspicious. Other cases should be followed up with US and clinically at 6-month intervals.

The rate of suspicious or nondiagnostic cytologic results has ranged from 5 to 23% (average, 10%) [19]. In our study, the suspicious cytology rate was 6.4% (9.4% per patients). The finding of "suspicious" cytology on FNAB of thyroid nodules is a dilemma for the endocrinologists. While numerous clinicians recommend surgical excisions for accurate diagnosis in these patients, certain authors mention that the malignancy rate in these lesions is low and patients might undergo unnecessary procedures. We found the histopathologically confirmed malignancy rate in suspicious cytology as 46.15%. FNAB cytology does not distinguish between Hürthle cell lesion/neoplasm and Hürthle cell adenoma and carcinoma. The malignancy rate in Hürthle cell neoplasm is quite variable and rates as high as 35% and as low as 14% are reported [30, 31]. Our rate was higher than in the literature (46.3%). Also, follicular lesion/neoplasm can not be distinguished from follicular adenoma or carcinoma cytologically. They are diagnosed as carcinoma according to vascular and capsular invasion histologically [32]. A retrospective analysis of surgical series demonstrated the malignancy rate in these patients as 18–47% [33, 34] in accordance to 37.5% in the present study. Rate of malignancy in lesions with suspicious cytology for papillary carcinoma was 52.7% in our series. Mittendorf et al. reported it as 40% [35]. Our results suggest that all lesions with suspicious cytology for malignancy should be accepted as malignant and evaluated in terms of surgery.

In conclusion, US have an important place in the evaluation of thyroid nodules. Malignancy risk could be determined according to US findings. Particularly, the risk is highest in case of a combination of margin irregularity, hypoechoic texture, and microcalcification. Nodule size alone is not a reliable indicator of a benign or malignant nature of a thyroid lesion. While performing FNAB procedure, US characteristics are more important than nodule size.

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