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Cytological and Ultrasound Findings in Indeterminate Lesions of the Thyroid Gland

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Abstract

Objectives: Thyroid nodules are common, and the majority are discovered incidentally on physical examination or imaging studies. Certain features on ultrasound (US) have been traditionally associated with malignant lesions and others with benign lesions. The aim of this study was to investigate the efficacy of US in determining malignancy in thyroid lesions diagnosed as indeterminate or malignant according to the cytological findings on fine needle aspiration biopsy (FNAB).

Methods: The records of 270 patients, referred to a single clinic with multinodular goiter were evaluated retrospectively, and 400 thyroid nodules sized larger than 5 mm in diameter were selected for the study. After exclusion of nodules classified as benign according to the FNAB findings, 203 thyroid nodules were included in this study. The nodules were divided into two groups on the basis of the FNAB findings: group 1 consisted of 82 nodules with indeterminate cytology and group 2 consisted of 121 nodules with cytological findings of malignancy or suspicious for malignancy.

Results: The diagnostic accuracy of ill-defined borders was 69.5% in group 1 (indeterminate) and 56% in group 2 (p=0.04). The diagnostic accuracy of solid composition was 50% in group 1 and 73% in group 2 (p=0.01). Positive correlation was demonstrated between ill-defined margins and malignant histology in group 1 (r=0.411, p=0.001), and between microcalcifications and malignant histology in group 2 (r=0.247, p=0.002).

Conclusions: In this study, the only US finding shown to be correlated with malignant histology in thyroid nodules of indeterminate cytology on FNAB was ill-defined margins. More precise US criteria are needed to decide on surgery in patients with thyroid nodules of indeterminate cytology.

Key words: *Thyroid nodule; ultrasonography; indeterminate cytology; ill-defined borders; microcalcifications*

Introduction

Thyroid nodules are a common clinical problem, with an estimated prevalence in the population of 4–7%. The majority of thyroid nodules are discovered incidentally on physical examination or imaging studies, particularly during ultrasound (US) of the neck [1].

US, which is a tool that is widely used in the assessment of thyroid nodules, is becoming progressively effective in the identification of lesions at higher risk of malignancy, according to specific US features. The features variously reported to be associated with malignancy include a rounded shape, ill-defined margins, mainly solid composition, microcalcificationsand intranodular vascular spots [2].

When a thyroid nodule is detected on physical examination or US, patients are advised to undergo fine needle aspiration biopsy (FNAB). FNA cytology is currently the most useful screening test in the evaluation of thyroid nodules [3]. It is a reliable, cost-effective method for the diagnosis of malignancy and results in the reduction of unnecessary thyroid surgery for benign nodules [4]. Although some US features have been traditionally associated with malignant lesions and others with benign lesions, no single characteristic is sufficiently reliable in nodules with indeterminate cytology on FNAB, such as those designated "atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)" and "follicular

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neoplasia/suspicious for follicular neoplasia" [5]. The aim of this study was to investigate the performance of US in determining malignancy risk in patients with indeterminate lesions and compare the US findings with those of malignant lesions.

Material and Methods

Patients

Between January 2015 and January 2016, 270 patients with multinodular goiter were referred forthyroidectomy to the Department of General Surgery at Bagcilar Training and Research Hospital, Istanbul-Turkey. The patients resided in an iodine deficient area. The records of these patients were evaluated retrospectively and the data on 400 thyroid nodules sized larger than 5 mm in diameter were retrieved and analyzed. Benign thyroid nodules according to the cytological findings on FNAB were excluded. The remaining 203 thyroid nodules were included in this study.

Total or subtotal thyroidectomy had subsequently been performed on all the study patients. The final histopathological diagnosis was determined by a single pathologist experienced in endocrine pathology, who was blinded to the US features.

The nodules were divided into two groups on the basis of the preoperative FNAB results: Group 1, consisting of 82 nodules with indeterminate cytology (AUS/FLUS, and follicular neoplasia/suspicious for follicular neoplasia), and Group 2 consisting of 121 nodules with malignant cytology or cytology suspicious for malignancy. The study protocol was reviewed and approved by the institutional ethical committee.

Ultrasonography

The US thyroid examinations for morphological study were performed with a digital US scanner equipped with a 11.4-MHz linear transducer (Sonoline Antares, Siemens, Erlangen, Germany).

The examinations were conducted and recorded by an experienced sonographer according to standard procedure. The following US parameters were assessed in all nodules: (i) echographic structure (solid, mixed or cystic); (i) echogenicity (iso-, hyper- or hypoechoic); (iii) presence or absence of microcalcifications; (iv) lesion margins (well-defined or blurred).

Preoperatively, the presence of calcified, solid, hypoechoic nodules and ill-defined nodule margins were considered to be indicative of malignancy. The strap muscles were uniformly present in all patients; therefore, the strap muscle was selected as the comparative standard for the evaluation of the echogenicity of solid nodules.

Statistical analysis

The clinical, US, cytological and histological findings were recorded separately and processed for blinded statistical evaluation. Analysis was performed with the statistical package SPSS 22.0 (SPSS, Chicago, IL). Differences between parameters were compared with the student's *t*-test. Frequency distributions were compared with the chi-square test. Univariate odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess the relationships between the US criteria and the histological findings. Results were considered statistically significant at $p<0.05$. The specific US criteria and final histopathological results of nodules were analyzed and compared. The numbers of true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) US diagnoses were determined. The diagnostic value of the US criteria was assessed in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy.

Results

The mean age of the patients undergoing surgery for a thyroid nodule was 46.4±12.7 (range 20-82) years, with a female/male ratio of 4.8/1. No difference was found in age and sex between the two groups. The histopathological examination revealed papillary thyroid carcinoma in 28 (34.1%) nodules in Group 1 (intermediate cytology on FNAB) and 112 (92.6%) nodules in Group 2 (malignancy or suspicious for malignancy on FNAB) (p=0.001). The US features of the nodules in the two groups are shown in Table 1.

When the US features and histopathological findings were evaluated together, the diagnostic accuracy of ill-defined borders of the thyroid nodule on US was determined to be 69.5% in Group 1 and 56% in Group 2 (p=0.04). The PPV was higher in Group 2 (p=0.001) and the NPV was higher in Group 1 (p=0.001) (Table 2).

The diagnostic accuracy of solid composition of the thyroid nodule on US was determined to be 50% in Group 1 and 73% in Group 2 (p=0.01). The PPV of solid composition was higher in Group 2 (p=0.001) and NPV was higher in Group 1 (p=0.001) (Table 3).

No significant differences between the two groups were found in the diagnostic accuracy of microcalcification and hypoechogenicity on thyroid nodule US in diagnosing malignancy.

Positive correlation was demonstrated between ill-defined margins on thyroid nodule US and malignant histology in Group 1 (r=0.411, p=0.001), and between microcalcification and malignant histology in Group 2 (r=0.247, p=0.002).

Table 1. *Ultrasound features of thyroid nodules according to cytological findings on fine needle aspiration biopsy (FNAB).*

	Ill-defined borders	Microcalcification	Solid composition	Hypoechogenicity	Malignancy
Group 1	41 (50%)	18 (22%)	61 (74.4%)	36 (43.9%)	28 (34.1%)
Group 2	65 (53.7)%	71 (58.7%)	94 (77.7%)	70 (57.9%)	112 (92.6%)
P	0.60	0.05	0.58	0.51	0.001

Group 1: indeterminate cytology, Group 2: cytology malignant or suspicious for malignancy, on FNAB

Table 2. *The significance of ill-defined borders on ultrasound (US) in predicting the malignancy of thyroid nodules.*

		Group 1 (n:82)	Group 2 (n:121)	P
Ill-defined borders	Sensitivity (%)	78.5	91	0.01
	Specificity (%)	64.8	66	NS
	PPV(%)	53.6	95	0.001
	NPV (%)	85	10	0.001
	Accuracy (%)	69.5	56	0.04

Group 1: indeterminate cytology, Group 2: cytology malignant or suspicious for malignancy on fine needle aspiration biopsy (FNAB)
PPV = positive predictive value, NPV = negative predictive value

Discussion

Indeterminate cytology on FNAB of a thyroid nodule constitutes a challenge in the clinical setting. In this study, the diagnostic performance of US in thyroid nodules with indeterminate cytology on FNAB was investigated and their US features were compared with those of nodules with malignant cytology.

In this study, the thyroid nodules were evaluated according to their US features and their histopathological findings, regardless of their size. There has been controversy regarding the significance of nodule size. In one prospective study conducted by Kim and colleagues [6], no statistically significant difference was found with regard to size between benign and malignant nodules in 155 patients with nonpalpable thyroid nodules who later underwent FNAB, while Sidawy and colleagues [7] reported a higher frequency of thyroid cancer in nodules larger than 4 cm.

Various US features have been reported to be related to an increased likelihood of thyroid cancer, including presence of calcifications, hypoechogenicity, irregular margins, absence of a halo, solid composition, and vascularity of the nodule. The sensitivity, specificity, and negative and positive predictive value for these criteria, however, showed no consistency between the different studies. No single US feature has been reported to show both high sensitivity and a high PPV value for thyroid cancer [8].

Ill-defined borders have been associated with thyroid cancer, with a sensitivity ranging from 17.4 to 77.5% and a PPV between 9.3 and 60.0% [9-11]. In the present study the diagnostic accuracy of ill-defined borders was 69.5% for Group 1 (indeterminate cytology), which was statistically higher than Group 2, and positive correlation was demonstrated with malignant histology in the indeterminate group.

Table 3. *The significance of solid composition on ultrasound (US) in predicting the malignancy of thyroid nodules*

		Group 1 (n:82)	Group 2 (n:121)	P
Solid composition	Sensitivity (%)	85.7	77	NS
	Specificity (%)	31.4	22	NS
	PPV (%)	39.3	92	0.001
	NPV (%)	81	7	0.001
	Accuracy (%)	50	73	0.01

Group 1: indeterminate cytology, Group 2: cytology malignant or suspicious for malignancy on fine needle aspiration biopsy (FNAB)
PPV = positive predictive value, NPV = negative predictive value

The US feature with the highest sensitivity (69 - 75%) in predicting malignancy was solid composition, but with a low PPV, as a solid nodule has only a 15.6 - 27% chance of being malignant [8]. In this study, solid composition of the nodule was the only characteristic with significantly higher diagnostic accuracy in Group 2, with a PPV of 92%, not unexpected, as this group had malignant cytology on FNAB. In group 1, with indeterminate cytology, the PPV of solid composition was 39.3%.

In the present study, the PPV of both hypoechogenicity and microcalcification was high in the malignant cytology group, 94% and 98% respectively. The diagnostic accuracy of hypoechogenicity was 51% and 58% for Group 1 and Group 2, respectively, and of microcalcification 53.6% and 64% for Group 1 and Group 2, respectively, with no significant difference between two groups in diagnostic accuracy.

Several authors have stated that hypoechogenicity is suggestive of malignancy; most thyroid nodules, however, have a hypoechoic character, and most of those are benign [12]. No correlation was found in this study between hypoechogenicity and malignant histopathology in either group, and the sensitivity was as low as 59%, even in the group with malignant cytology on FNAB.

The feature shown to have the highest PPV for diagnosing malignancy, in the range of 41.8 - 84.2%, is the presence of microcalcifications; however, as microcalcifications are only found in 26.1 - 59.1% of thyroid cancers, they are of low sensitivity [9,10]. Solbiati and colleagues [13] suggest that detection of microcalcifications in thyroid nodules with high-frequency US can be considered almost specific for malignancy.

In the present study, the sensitivity of microcalcifications was 14.2% in the indeterminate cytology group and 62% in the malignant group. Correlation was demonstrated between microcalcifications and malignant histopathology in the group with malignant cytology on FNAB, but not in the indeterminate group.

Conclusion

The results of the present study reveal that more precise criteria are needed to recommend surgery in patients with indeterminate cytology on FNAB of thyroid nodules. No specific US criterion was shown to indicate malignancy in thyroid nodules with indeterminate cytology on FNAB with 100% reliability; ill-defined margins was the only US feature to show positive correlation with malignant histology in the group with indeterminate cytology. The combination of these features may improve the PPV value of US to some extent.

This conclusion has implications in clinical practice, since it can help in the better selection of patients with thyroid nodules for FNA and, more importantly, in the decision of when surgery is indicated for nodules with indeterminate cytology.

Ethical Approval: *All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.*

Conflict of Interest: *The authors declare that they have no conflict of interest.*

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