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ULTRASONOGRAPHY AND DUPLEX DOPPLER ULTRASONOGRAPHY BASED INDICES IN NODULAR THYROID DISEASE

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Abstract

Background. Fine needle aspiration biopsy (FNAB) is an important tool in the diagnosis of thyroid nodules.

Aim. Our aim was to investigate the malignancy criteria in thyroid nodules by gray-scale ultrasonography (US) and duplex Doppler ultrasonography (DDUS), and their usefulness in reducing the number of unnecessary FNAB's.

Study design. This was a prospective observational study.

Subjects and methods. 181 benign and 18 malignant thyroid nodules were evaluated by US and DDUS before FNAB or thyroidectomy. US was used to note size, shape, internal structure, nodule echogenicity, marginal properties, peripheral hypoechogenic halo, and microcalcifications. DDUS studies were used to evaluate the maximum and minimum flow velocity (V_{max} and V_{min}), systolic/diastolic flow velocity ratio (S/D), pulsatility index (PI), resistive index (RI), acceleration time (AT) and acceleration value.

Results. Contour irregularity, size and presence of microcalcifications ($p<0.001$, $p=0.02$ and $p=0.002$, respectively) and S/D, V_{min}, PI, RI and AT were significantly different ($p=0.004$, $p=0.007$, $p=0.032$, $p=0.003$ and $p=0.003$, respectively) were significant for malignant nodules. Benign and malignant nodules with or without suspicious US findings had similar DDUS findings. V_{max}, V_{min}, PI, RI, and AT were significantly different in the presence of microcalcification ($p=0.043$, $p=0.001$, $p=0.031$, $p=0.04$, and $p=0.019$ respectively). AT was significantly different in the case of absence of microcalcification ($p=0.019$). Comparing the irregular margins, V_{min}, PI and RI were significantly different ($p=0.014$, $p=0.003$, and $p=0.014$ respectively).

Conclusion. Benign and malignant thyroid nodules can be differentiated using gray-scale US findings and DDUS based indices together to reduce the number of unnecessary FNAB's.

Key words: thyroid, thyroid cancer, ultrasonography, duplex Doppler ultrasonography, thyroid nodule, acceleration time.

INTRODUCTION

Nodular thyroid disease is commonly found in clinical practice

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and its prevalence is increasing as ultrasound technology advances. The main concern in nodular disease is an underlying neoplastic disease. The incidence of thyroid carcinoma is 5-15% and is independent of nodule size and number (1, 2). Several studies suggested that thyroid gray-scale ultrasonography (US) could differentiate benign from malignant thyroid nodules, but currently much debate exists as to whether such features have been successfully identified.

Among several gray-scale US characteristics, hypoechogenicity, microcalcifications, irregular or microlobulated borders and absence of halo have been widely studied in retrospective studies and were reported to be useful in predicting thyroid malignancy, but are associated with low sensitivity or specificity (1-5).

A recent consensus statement only reported a sensitivity of 54–74% and a specificity of 79–81% for the detection of malignancy by color Doppler US (CDUS) (6). However, some investigators were unable to demonstrate the value of CDUS for the prediction of malignancy (7,8). Therefore, the usefulness of this technique in predicting the malignancy of thyroid nodules is still controversial.

In this prospective study, we aimed to show gray-scale US characteristics and to determine spectral Doppler US waveform characteristics of thyroid nodules, which could be related to malignancy in thyroid nodules and their usefulness to reduce the number of unnecessary fine needle aspiration biopsies (FNABs).

MATERIALS AND METHODS

Patients

This prospective observational study was approved by the Institutional Review Board and informed written consent was obtained from all of the reviewed subjects. Patients with nodular disease who were admitted to our General Surgery and Endocrinology clinics were within the scope of this study. Diagnosis was established by FNAB or histopathological evaluation of thyroidectomy material. The reasons for surgery were: hyperthyroidism, increase in the number and/or size of nodules, compression symptoms due to nodules and suspicious or malignant cytology. FNAB was performed on nodules greater than 10 mm in size or which had suspicious properties on gray-scale US.

FNAB was performed on 128 nodules, and 56 patients (86 nodules) underwent thyroidectomy. The patients that underwent surgery were biopsied in another center and we did not include those FNAB results in our study.

Equipment and scanning

The gray-scale US and duplex Doppler ultrasonography (DDUS) studies were performed using a 13-5 MHz linear matrix array probe (Antares Acuson Premium Edition, Siemens Medical Solutions, Erlangen, Germany) by one radiologist to be able to standardize the examination, who was also unaware of the FNAB results or reason for surgery when performing the study. Patients were examined in the supine position with the head in hyperextension. Patients were asked to hold their breath and not to swallow during the DDUS examination. Nodule size was measured and defined as the maximum dimension of the thyroid nodule. Gray-scale US was used to evaluate nodule characteristics, including shape, internal structure, marginal properties, presence of a peripheral halo, and presence of intranodular microcalcifications. DDUS was performed on two different arteries with the largest diameters available; one at the periphery and one at the center of each nodule. For each nodule, an appropriate pulse repetition frequency, wall filter setting and sample volume was used for a given waveform and vessel diameter, respectively. Doppler angle was kept between 45 and 60 degrees. Spectral Doppler US waveform characteristics were noted for maximum flow velocity (V_{max} - cm/sec), minimum flow velocity (V_{min} – cm/sec), systolic / diastolic flow velocity (S/D) ratio, pulsatility index (PI) (systolic flow velocity - diastolic flow velocity / mean velocity), resistive index (RI) (systolic flow velocity - diastolic flow velocity / systolic flow velocity), acceleration time (AT - sec) (time between end diastolic flow to peak systolic flow) and acceleration value (cm/sec^2) (systolic flow velocity - diastolic flow velocity / acceleration time). A minimum of 3 spectral Doppler waveforms were acquired for each spectral analysis. The mean values of two spectral waveform analyses were used to assess V_{max}, V_{min}, S/D ratio, PI, RI, AT and acceleration values. Measurements were taken manually and the US equipment calculated the Doppler parameters automatically (Fig. 1 a, b).

FNAB was performed with US guidance (Logic 700 GE Medical Systems, Milwaukee, USA) with a 7-9 MHz linear array probe by two experienced interventional radiologists who were blinded to the DDUS findings of the nodules. A cytopathologist was present for every aspiration. The probe was put in a sterile cover and local anesthetic was applied to the biopsy site. Aspiration was done with 22 G needles, and US guidance was used in real time. Negative pressure aspiration was performed with a 10 ml syringe. The pressure was normalized before the exit, and the biopsy site was compressed for homeostasis after needle withdrawal. An average of 5 aspirations was performed on each thyroid nodule to sample it adequately.

Aspiration material was projected on two glass slides. Thin preparations were made using another slide at 45 degrees. The materials were assessed for adequacy by the cytopathologist for every single aspiration and the procedure was ended when the cytopathologist was satisfied with the amount and quality of the material. Hematoxylin-Eosin and Papanicolaou dyes were used before evaluation with a light microscope. Cytopathological evaluation focused on cell density, cell size, pleomorphism, cohesion, nucleus/cytoplasm ratio, nucleus characteristics, chromatin characteristics, necrosis, and the presence of inflammatory cells. Final cytopathological diagnosis was classified according to the Bethesda System for reporting thyroid cytopathology (9).

Surgery was performed as total thyroidectomy, subtotal thyroidectomy

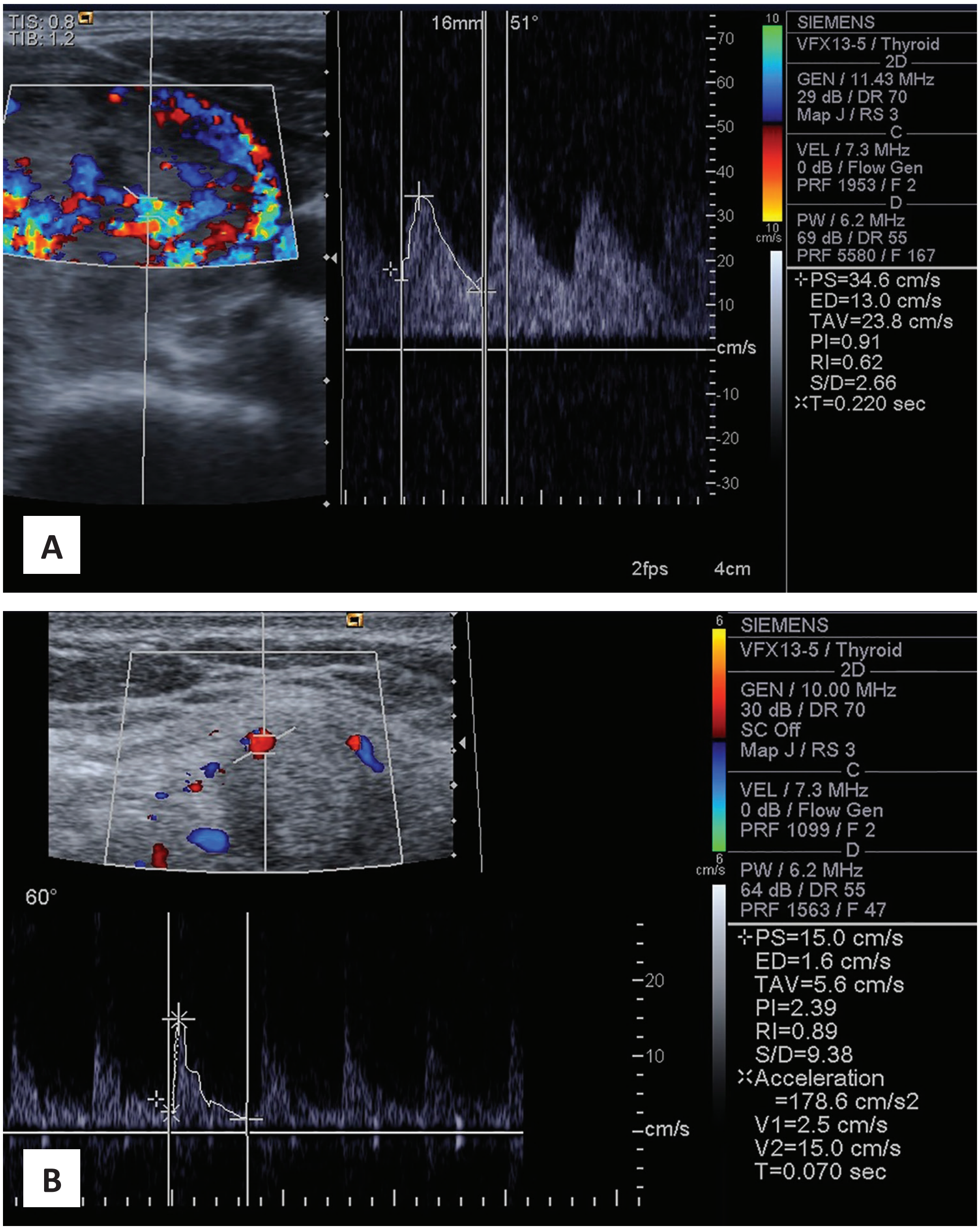

Figure 1. A. DDUS of a benign thyroid nodule (Histopathological diagnosis was nodular hyperplasia). B. DDUS of a malignant thyroid nodule (Histopathological diagnosis was papillary carcinoma).

(right - left lobectomy, isthmusectomy), or nodulectomy. Pathological evaluation covered all the nodules in the surgical material. Results included hyperplasias (nodular hyperplasia (adenomatous or nodular goiter), diffuse hyperplasia (Grave's disease), follicular adenoma (solitary adenomatous or adenomatous nodule), papillary carcinoma, and follicular carcinoma. All lesions were histopathologically classified according to World Health Organization criteria (10).

Statistical analysis

Histopathological and cytopathological diagnoses were used to group thyroid nodules into two classes, as benign nodules (colloid nodules, nodular or diffuse hyperplasias) or malignant nodules (papillary carcinoma, follicular carcinoma, medullary carcinoma) for statistical analysis. Groups were compared for size, shape, internal structure, nodule echogenicity, marginal properties, presence of a peripheral hypoechogenic halo and microcalcifications in the nodules, V_{max}, V_{min}, S/D ratio, PI, RI, AT and acceleration values of the nodules. We further grouped the DDUS findings of malignant and benign nodules according to the presence or absence of microcalcification and smooth or irregular margins. Statistical analyses were made using Chi-square test and Chi-square Fisher's exact test. Receiver operating characteristic (ROC) analysis was used to evaluate continuous variables. The benign nodule group was used as a reference for ROC analysis. The mean values between groups were compared using Student t-test and Mann-Whitney U tests. Logistic regression analysis for DDUS findings was evaluated separately with the presence of microcalcification and irregular margins, with malignancy as the dependent variable. This was done to determine whether suspicious US findings were independent of each other and DDUS findings in predicting malignancy in thyroid nodules. Statistical significance was set as $p < 0.05$ and bidirectional.

RESULTS

FNAB materials were inadequate for diagnosis in 15 patients and were excluded from the study. The study included 145 patients (124 females, 21 males) with an age range of 21 to 87 (mean: 47.5 ± 13.59) years. Of the 199 nodules included in this study, 181 were benign and 18 were malignant and diagnosis was established in 113 nodules by fine-needle aspiration cytopathology and by histopathological evaluation of thyroidectomy material in 86 nodules. Cytopathological diagnoses were reported as colloidal nodule in 5 cases and hyperplastic in 108 nodules. Evaluation of the thyroidectomy material resulted in a diagnosis of papillary carcinoma in 12 nodules, follicular carcinoma in 5, medullary carcinoma in one, colloidal nodule in 3 and nodular hyperplasia in 65 nodules.

We could not evaluate V_{min}, S/D ratio, PI, RI in 1 benign and 2 malignant nodules due to a triphasic flow pattern that had reverse diastolic flow. Gray-scale US and DDUS findings of benign and malignant nodules are presented in Table 1 and Table 2.

The presence of irregular margins, size (< 1 cm) and presence of microcalcifications were higher in malignant nodules, which was statistically significant ($p<0.001$, $p=0.02$ and $p = 0.002$, respectively) (Table 1). Irregular margins had a sensitivity of

Table 1. Gray scale ultrasonographic findings of benign and malignant nodules

Ultrasonographic findings		Benign Nodules (n=181)	Malignant Nodules (n=18)	p
Size	<10 mm	10 (5.52%)	4 (22.22%)	0.02
	10-14 mm	30 (16.57%)	3 (16.67%)	
	≥ 15 mm	41 (77.9%)	11 (61.11%)	
Shape	Round	16 (8.84%)	4 (22.22%)	0.18
	Oval	135 (74.59%)	12 (66.67%)	
	Irregular	3 (16.57%)	2 (11.11%)	
Internal structure	Solid	118 (65.59%)	15 (83.3%)	0.34
	%75 solid	40 (22.1%)	3 (16.67)	
	Semisolid	20 (11.05%)		
	Cystic	3 (1.66%)		
Nodule echogenicity	Hypoechogenic	113 (62.43%)	14 (77.78%)	0.49
	Hyperechogenic	35 (19.34%)	3 (16.67%)	
	Isoechogenic	12 (6.63%)		
	Mixed	21 (11.6%)	1 (5.56%)	
Marginal properties	Smooth	118 (65.19%)	3 (16.67%)	< 0.001
	Irregular	63 (34.81%)	15 (83.3%)	
Peripheral hypoechogenic halo	None	83 (45.86%)	10 (55.56%)	0.37
	Incomplete	10 (5.52%)	2 (11.11%)	
	Complete	88 (48.62%)	6 (33.3%)	
Microcalcifications	None	139 (76.79%)	7 (38.89%)	0.002
	Present	42 (23.2)	11 (61.1%)	

Values are presented as number (%).

83%, a specificity of 65%, a positive predictive value (PPV) of 19% and a negative predictive value (NPV) of 95% for malignancy. Microcalcifications had a sensitivity of 61%, specificity of 76%, PPV of 20%, and NPV of 95% for malignancy. Shape, internal structure, nodule echogenicity and the presence of a peripheral hypoechogenic halo were not found to be significantly different in benign and malignant nodules (Table 1).

V_{min}, S/D ratio, PI, RI, and AT were significantly different in malignant nodules (p = 0.007, p = 0.004, p = 0.003, p = 0.003, and p = 0.032, respectively). There were no significant differences based on Vmax or acceleration values (Table 2). ROC analysis showed V_{min}, S/D, PI, RI and AT variables to be significantly different for malignancy (Table 3). Sensitivity, specificity, PPV and NPV's were based on values calculated by ROC analysis (Table 4).

Benign nodules with or without suspicious US findings had similar DDUS findings. This was also valid for malignant nodules. When we compared DDUS findings of benign and malignant nodules according to the presence of microcalcification, V_{max}, V_{min}, PI, RI,

Table 2. DDUS flow values and ratios of benign and malignant nodules

	Benign nodules		Malignant nodules		
	Number	Mean (±SD)	Number	Mean (±SD)	p
Vmax	181	36.33 ± 17.61	18	28.93 ± 12.56	0.136
Vmin	180	14.17 ± 8.43	16	8.4 ± 4.52	0.007
S/D ratio	180	2.97 ± 1.36	16	4 ± 1.93	0.004
PI	180	0.99 ± 0.3	16	1.29 ± 0.42	0.003
RI	180	0.62 ± 0.12	16	0.71 ± 0.11	0.003
AT	181	0.18 ± 0.06	18	0.15 ± 0.05	0.032
A	181	138.93 ± 96.53	18	163.31 ± 99.64	0.219

Vmax: Maximum flow velocity (cm/sec), Vmin: Minimum flow velocity (cm/sec), S/D: Systolic/Diastolic flow velocity ratio, PI: Pulsatility index, RI: Resistive index, AT: Acceleration time (sec), A: Acceleration (cm/sec²).

Table 3. Area under the curve in ROC analysis of the DDUS findings

Test Result Variable(s)	Area	Std. Error(a)	Asymptotic Sig. (b)	Asymptotic 95% CI	
				Lower Bound	Upper Bound
Vmax	0.610	0.068	0.146	0.476	0.744
Vmin	0.705	0.057	0.007	0.593	0.817
S/D ratio	0.281	0.064	0.004	0.155	0.407
PI	0.272	0.062	0.003	0.151	0.394
RI	0.279	0.063	0.003	0.155	0.403
AT	0.646	0.069	0.053	0.511	0.781
A	0.439	0.071	0.422	0.301	0.578

Vmax: Maximum flow velocity (cm/sec), Vmin: Minimum flow velocity (cm/sec), S/D: Systolic/Diastolic flow velocity ratio, PI: Pulsatility index, RI: Resistive index, AT: Acceleration time (sec), A: Acceleration (cm/sec²), CI: Confidence interval.

Table 4. Threshold values of Vmin, S/D ratio, PI, RI and AT according to ROC analysis

DDUS parameters	Threshold values	Sensitivity	Specifity	PPV	NPV
Vmin	7.8 cm/sec and below	68.3%	62.5%	64.5%	66.3%
S/D ratio	4.065 and above	86.7%	31.3%	55.7%	70.1%
PI	1.295 and above	83.3%	37.5%	57.1%	69.1%
RI	0.715 and above	79.4%	37.5%	55.9%	64.5%
AT	0.14 sec and below	71.7%	43.7%	56%	60.6%

Vmin: Minimum flow velocity (cm/sec), S/D: Systolic/Diastolic flow velocity ratio, PI: Pulsatility index, RI: Resistive index, AT: Acceleration time (sec), ROC: Receiver operating characteristic, DDUS: Duplex Doppler ultrasonography, PPV: Positivite predictive value, NPV: Negative predictive value.

and AT were significant (p = 0.043, p= 0.001, p = 0.031, p = 0.04, and p = 0.019 respectively) (Table 5). In the case of absence of microcalcification, mean AT was significantly different between benign and malignant nodules (p = 0.019). Mean V_{min}, PI and RI values were significantly different between benign and malignant nodules, compared with the irregular margins (p=0.014, p=0.003, and p = 0.014 respectively) (Table 5).

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Table 5. DDUS findings of thyroid nodules comparing the presence or absence of microcalcification and smooth or irregular margin

		Microcalcification			Marginal properties			
		Malignant nodules (mean ± SD)	Benign nodules (mean ± SD)	p		Malignant nodules (mean±SD)	Benign nodules (mean±SD)	p
V_{max}	Present	27.9 ± 5.3	37.2 ± 1.9	p=0.043	Smooth	35.2 ± 2.47	35.95 ± 1.9	p>0.05
	Absent	30.54 ± 9.19	36.06 ± 14.84	p>0.05	Irregular	27.68 ± 3.88	37.02 ± 15.27	p>0.05
V_{min}	Present	7.89 ± 0.77	13.28 ± 1.06	p=0.001	Smooth	11.15 ± 7.14	14.1 ± 0.14	p>0.05
	Absent	9.52 ± 6.78	14.07 ± 6.85	p>0.05	Irregular	8 ± 1.34	14.26 ± 4.45	p=0.014
S/D	Present	3.87 ± 0.51	3.07 ± 0.08	p>0.05	Smooth	3.62 ± 0.27	2.92 ± 0.22	p>0.05
	Absent	4.25 ± 4.82	3.08 ± 0.45	p>0.05	Irregular	4.04 ± 0.03	3.04 ± 0.11	p>0.05
PI	Present	1.26 ± 0.24	1.01 ± 0.01	p=0.031	Smooth	1.24 ± 0.08	0.99 ± 0.07	p>0.05
	Absent	1.34 ± 1.01	1.02 ± 0.14	p>0.05	Irregular	1.29 ± 0.01	0.98 ± 0.07	p=0.003
RI	Present	0.71 ± 0.1	0.62 ± 0.01	p=0.04	Smooth	0.72 ± 0.02	0.61 ± 0.02	p>0.05
	Absent	0.7 ± 0.19	0.61 ± 0.04	p>0.05	Irregular	0.7 ± 0.007	0.61 ± 0.04	p=0.014
AT	Present	0.16 ± 0.01	0.17 ± 0.007	p>0.05	Smooth	0.16 ± 0.02	0.18 ± 0.02	p>0.05
	Absent	0.13 ± 0.07	0.18 ± 0.04	p=0.019	Irregular	0.14 ± 0.02	0.17 ± 0.05	p>0.05
Acceleration (cm/sec²)	Present	138.09 ± 46.24	149.95 ± 5.72	p>0.05	Smooth	166.36 ± 16.29	135.04 ± 52.25	p>0.05
	Absent	202.94 ± 53.91	135.59 ± 0.49	p>0.05	Irregular	162.7 ± 28.67	146.21 ± 19.65	p>0.05

V_{max}: Maximum flow velocity (cm/s), V_{min}: Minimum flow velocity (cm/s), S/D: Systolic/Diastolic flow velocity ratio, PI: Pulsatility index, RI: Resistive index, AT: Acceleration time (s).

regression analyses, the presence of microcalcification and irregular margins were related independently with malignancy (p was between 0.002 - 0.006 and 0.001 - 0.003, B was between B [-1.5] - [-1.95] and [-2.09] - [-2.53] respectively). DDUS findings of V_{min}, S/D, PI and RI values were also related independently with malignancy (p = 0.019, p = 0.038, p = 0.004, p = 0.011 and B = 0.864, B = 1.388, B = 10.185, B = 774.15 respectively).

DISCUSSION

Nodular disease of the thyroid is a frequent disorder. Although malignant nodules occur at low frequency, they constitute the largest group of endocrine malignancies developing from the follicular epithelium, with about 122,000 new cases every year (11). The recommended examination for thyroid nodule scanning is gray-scale US. FNAB has an important role in the diagnosis of thyroid nodules (12), with a false negative rate of 0-1% and a false positive rate of less than 5% (2,13). Wide use of FNAB has also decreased unnecessary thyroidectomies (9).

FNAB requires sufficient material to be obtained, an experienced cytopathologist, an experienced clinician and imaging guidance (6, 14). The aim of gray-scale US scanning is to reduce the number of unnecessary FNAB's based on solid gray-scale US imaging criteria.

There is no evidence in the literature to suggest that malignancy is based on nodule size (1, 2, 15, 16). In our study we found a nodule size of less than 1 cm to be significant for malignancy. Nodules smaller than 1 cm, with non-suspicious gray-scale US patterns are conceivably not submitted to FNAB. We are a referring center, where we evaluate and biopsy many nodules less than 1cm in size with suspicious gray-scale US findings. This may be the reason why we detected a higher rate of malignancy in small nodules. Therefore, we do not believe this finding to be of importance in detecting malignant thyroid nodules.

In our study, we found the shape, hypoechogenicity and internal architecture of nodules and the presence of a hypoechogenic rim to be of no significant value in detecting malignancy. There are different opinions about the shape of the nodules. Kim *et al.* (16) studied 823 nodules and suggested a round and oval shape to be more common for benign nodules. Alexander *et al.* (17), in contrast, reported a round shape to be more suggestive of malignancy. We, too, found a round shape more frequently for malignant nodules. However, this was not statistically significant. Hypoechogenicity of the nodule is regarded to be indicative of malignancy (2, 5, 16-22). In our study, however, the benign nodules in our study were mostly hypoechogenic (62.43%), and this was seen for 77.78% of malignant nodules with no statistically significant difference. In concordance with the literature, in our study, isoechogenic nodules did not harbor malignancy. Internal echo structure is also a predictor of malignancy, as solid or mostly solid nodules have been shown to have greater risk, and solid structure is documented to be the most sensitive aspect in a lesion (1, 2, 16, 20, 23). But, we did not find a correlation between malignancy and a solid or mostly solid internal echostructure.

Marginal irregularity is an important finding for local invasion and a risk factor for malignancy (1, 2, 16, 21, 22). Our findings are supportive of the literature. The most valuable positive predictor of malignancy is the presence of microcalcifications within the nodule (1, 2, 7, 16, 18, 20-24). Our study group had microcalcifications in 23.2% of benign and 61.11% of malignant nodules. We utilized the recommendations of the American College of Radiology to define all micro-echogenicities as calcifications, whereas the aforementioned studies used a posterior shadow as a criterion. This might explain why we found more microcalcifications in benign nodules. Microcalcifications are not the only reason for increased echogenicity on ultrasound images. Walls of vessels, fat, and tissues with high reflectivity to sound and air are also seen as echogenic structures. Calcifications produce shadowing behind them. We believe that this posterior shadow is the most useful clue for detecting microcalcifications in a thyroid nodule.

Presence of a complete hypoechogenic halo around the nodule is suggestive of a benign nature (7, 11, 22, 25). In our study complete hypoechogenic halo was found in 33.33% of malignant nodules, although there was no statistically significant difference between benign and malignant nodules.

The important role of angiogenesis in the growth of neoplastic or non-neoplastic masses has been shown in experimental and clinical studies (26). Angiogenesis increases the blood flow to the mass and helps with the growth of the tumor. On the other hand, angiogenesis plays an important role in predicting treatment response and prognosis. CDUS can demonstrate an increase in blood supply (27). The effect of angiogenesis has been studied by measuring flow velocity and indices using DDUS in malignant nodules (27-31). Doppler based indices have been developed to quantify changes in the waveform, which are the RI, PI and S/D ratio. These have the advantage that they can be used in situations where accurate angle correction, and thus velocity estimation, is not possible. The RI and PI reflect the degree of distal resistance, so that with increased peripheral resistance, as may occur with acute occlusions, the RI tends toward a value of 1.0, whereas the PI tends toward values of 1.0 or more.

We have detected no statistically significant difference between benign and malignant nodules based on V_{max} values. V_{min} values, on the other hand, were significantly different between the two groups. We also found indicators for increased resistance in malignant nodules, such as an increase in S/D ratio, PI and RI. Miyakawa *et al.* reported an increase in the S/D ratio in follicular carcinoma and presented a ROC curve analysis with an 88.5% sensitivity for follicular carcinoma when the S/D ratio was above 3.79 (31). Miyakawa *et al.* also showed that PI values were significantly different between benign nodules and follicular carcinoma, and ROC curve analysis showed a PI value over 1.35 was 89.8% sensitive for follicular carcinoma (31). Tamsel *et* *al.* showed that the value of RI was not significantly different between benign and malignant nodules (28). But De Nicholas *et al.* demonstrated that high RI values in follicular cancers were important determinants of malignancy and an RI threshold of 0.75 or above had a sensitivity of 91% and specificity of 40% for malignancy (27). De Nicholas *et al.*, and similarly Yang *et al.*, showed that the RI value of benign nodules was low (27,29). Ivanac *et al.* found that the RI value of malignant nodules (mean 0.75 ± 0.08) was higher than that of benign nodules (mean 0.56 ± 0.09) (30). They found the sensitivity and specificity of RI values equal or greater than 0.70 to be 80% and 92%, respectively (30). Mikayawa *et al.* (31) showed that an RI value of 0.78 or higher was seen in follicular carcinomas, with a sensitivity of 88.7% (31). In line with the literature, we found the S/D ratio, PI and RI to be elevated in malignant nodules. Vascular resistance is expected to be low in malignant and neoplastic nodules due to angiogenesis and an abnormal increase in vascularization (28). Our findings indicate an increased resistance in malignant nodules, contradicting this notion. The most possible explanation for this discrepancy is the high rate of occlusions, stenosis, and fistula in revascularized differentiated thyroid carcinomas (28). The V_{min} value is affected by the Doppler insonation angle, whereas the S/D ratio, RI and PI are not. Because they are reproducible and simple to perform, we think that these indices will be valuable in the search for malignancy in thyroid nodules.

Because of their possible value in the evaluation of flow resistance in neoplastic tissues, acceleration values and AT were studied in breast neoplasms. While Mesaki *et al.* found AT to be of use in breast malignancies, Özdemir *et al.* did not find the acceleration index to be of value (32,33). There are no studies in the literature regarding thyroid nodule AT and acceleration values. We presumed that as for V_{min}, S/D ratio, RI and PI, AT and acceleration values could be of value in the evaluation of flow resistance in malignant thyroid nodules. In our study, AT values of nodules were significantly different between the two groups and were lower in malignant nodules compared to benign ones. This may indicate a proximal stenosis in benign nodules. However, we do not have data to compare AT and acceleration values between benign nodules and normal thyroid tissue. The reason for this difference between benign and malignant nodules might be due to the defective vascular wall structure and an increased vascular flow in malignant nodules.

In our study, we found that microcalcification, irregular margin, V_{min}, S/D, PI, and RI values were related independently, and AT was related dependently with malignancy in thyroid nodules. When we compared the DDUS findings of benign and malignant nodules according to the presence or absence of microcalcification and irregular margin, V_{max}, V_{min}, PI, RI, and AT values were significantly different. But the presence or absence of microcalcification and irregular margin did not affect spectral Doppler US waveform analysis for both benign and malignant nodules.

This may indicate that suspicious US findings should not be used for predicting malignancy in thyroid nodules alone, although the presence of microcalcification and irregular margin had high sensitivity and specificity values. When it comes to DDUS parameters, they have low specificity values for detecting malignancy and this should restrain physicians from using them alone. We think that one should perform both gray-scale US and DDUS at the same time and use data from both to evaluate thyroid nodules for a FNAB decision. Further studies with larger numbers of malignant and benign nodules comparing DDUS based indices with or without US findings in the same group of patients would be beneficial for characterization of thyroid nodules.

LIMITATIONS

Our study population of malignant nodules was relatively small and inhomogeneous. Second, the nodules for which we performed FNAB had benign cytopathology results. Third, we could not rule out the effect of systemic diseases on the flow resistance of thyroid nodules, which we assumed to be relatively insignificant. Also, gray-scale US and DDUS examinations were performed by one examiner. This prevented us from performing inter and intraobserver analyses to demonstrate the reproducibility and value of our criteria.

In conclusion, neither gray-scale US findings nor DDUS based indices alone are enough for a FNAB decision. Benign and malignant thyroid nodules can be differentiated using gray-scale US findings and DDUS based indices together to reduce the number of unnecessary FNAB's.

Conflict of interest

We declare that there is no conflict of interest.

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Abbreviations

PS: Peak systolic flow velocity (cm/sec), ED: End diastolic flow velocity (cm/sec), TAV: Time average velocity (cm/sec), PI: Pulsatilite index, RI: Resistance index, S/D: Systolic/Diastolic flow velocity ratio, T: Acceleration time (sec).

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