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Araştırma Makalesi / Research Article

Ultrasonographic and Color Doppler Ultrasonographic Parameters to Discriminate Thyroid Nodules

Tiroid Nodüllerinde Ultrasonografi ve Renkli Doppler Ultrasonografi Bulguları Birlikteliğinde Malignite Saptanması

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Objective: To determine parameters that can be used to predict malignant thyroid nodules by using gray-scale ultrasonography and color Doppler ultrasonography

Materials-methods: Gray-scale ultrasonography and color Doppler ultrasonography findings were retrospectively analyzed in 60 nodules with known histopathology. Of 60 nodules, 12 nodules were malignant. The evaluation criteria for gray-scale ultrasonography were: size, echotexture, internal morphology, contour, presence of microcalcification, and presence of halo sign. The evaluation criteria for color Doppler ultrasonography were: vascular flow pattern and resistive index. Vascular flow patterns were classified as Types I, II, III, and IV.

Results: Irregular contour and type IV flow patterns were the most significant independent predictors of malignancy in malignant thyroid nodules. Resistive index was significantly higher in malignant nodules. The cut off value was established as resistive index ≥0.69; 91% sensitivity and 97% specificity were calculated in the identification of malignant nodules. A combination of the absence of a halo sign, type IV flow pattern, and irregular contour had the highest specificity and positive predictive value (66.7% sensitivity, 100% specificity, 100% positive predictive value, 92.3% negative predictive value).

Conclusion: We believe that by the integration gray-scale ultrasonography with color Doppler ultrasonography findings, it is possible to determine which nodule is malign/benign without performing fine needle aspiration biopsy (FNAB) and unnecessary operations could be prevented.

Key Words: ***Thyroid Nodule, Ultrasonography, Doppler Ultrasonography, Resistive Index, Vascularization***

Amaç: Tiroid nodüllerinde ultrasonografi bulgularına ek olarak renkliDoppler ultrasonografi bulguları ile birlikte malign - benign ayrımını yapabilmek

Materyal - Metod: Çalışmamızda total yada subtotaltiroidektomi sonucunda patolojileri bilinen 60 nodül incelenmiştir. Retrospektif olarak 60 nodülün 12'si malign karakterdeydi. Nodüllerde ultrasonografi bulguları olarak; boyut, ekojenite, natür, kenar yapısı, mikrokalsifikasyon varlığı, periferikhalo varlığı değerlendirilmeye alındı. Renkli Doppler ultrasonografi bulguları olarak kanlanma desenlerine ve rezistif indeks değerlerine bakıldı. Kanlanma desenleri 4 sınıfta gruplandırıldı; tip I, tip II, tip III, tip IV .

Bulgular: Düzensiz kenar yapısı ve tip IV kanlanma deseni malignnodül saptamada en özgül bağımsız parametreler olarak saptandı. Rezistif indeks değeri malignnodüllerde daha yüksek bulundu. Rezistif indeks için cutoff değeri % 91 duyarlılık ve % 97 özgüllük ile 0,69 olarak hesaplandı. Düzensiz kenar yapısı, periferikhalo kaybı ve tip IV kanlanma deseni kombinasyonu malignnodül saptamada en özgül ve en yüksek pozitif tahmini değere sahip bulgu olarak bulundu (% 66.7 duyarlılık, %100 özgüllük, %100 pozitiftahminideğer, %92.3 negatif tahmini değer).

Sonuç: Ultrasonografik ile renkli Doppler ultrasonografi bulguları birlikte malign – benign nodül ayrımı yapılabilir ve gereksiz cerrahi işlem engellenilebilir.

Anahtar Sözcükler: ***Tiroid Nodülü, Ultrasonografi, Renkli Doppler Ultrasonografi, Rezistif İndeks, İnternal Kanlanma***

Thyroid nodules are the most common thyroid disease with increasing prevalence, especially in iodine deficient areas (1). Ultrasound (US) is the primary and the most effective imaging modality in screening thyroid disease. Incidental thyroid nodules detected by US at an approximate rate of 70% of the population and detected by autopsy at a rate of approximately 50% in adults.(2). A great majority of thyroid nodules are benign. Approximately 4-14% nodules are malignant.(3).

In the literature, several studies reported that the most efficient method in discriminating between benign and malignant nodules is fine needle aspiration biopsy (FNAB) with a sensitivity of 65-98% and specificity of 72-100%.(4). Even in large,

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experienced centers inadequate specimen and non-diagnostic cytology rate is up to 15-20% (5,6). Furthermore, false negative results are reported at a range of 3-21%.(7). Consequently, a non-invasive, safe, and low cost diagnostic procedure is required, with high accuracy, to discriminate malignant and benign thyroid nodules. Several gray-scale US and color Doppler ultrasonography (CDUS) features have been reported to be highly suggestive of malignancy such as hypoechogenicity, presence of microcalcification, irregular contour, hypervascular central flow, and high Resistive Index (RI) (3,8,9). On the contrary, several authors claim that there are no correlations with the central flow, echogenicity, shape, and malignancy (9,11).

The purpose of this study is to evaluate the capabilities of gray-scale US and CDUS alone and in combination, in detecting malignant thyroid nodules. Furthermore, this study also aimed to determine which thyroid nodule should receive surgery using the US and CDUS parameters without performing FNAB.

Materials and Methods

The researchers of the current study retrospectively reviewed the records of patients who were underwent surgical intervention between the years 2004 and 2009. Thirty patients' (median age: 42.37±10.10 years; range: 25-61), consisting of 24 women (80%) and 6 men (20%), gray-scale US and CDUS data were evaluated by one radiologist. Sixty nodules were included in the study. Each nodule was reported as benign or malignant nodule based on histologic classification. Out of 60 nodules, 48 (80%) nodules were benign and 12 (20%) nodules were malignant. All US and CDUS were conducted by the same radiologist with more than ten years of experience in thyroid ultrasound. Sonography was performed using the Sonoline Antares system (Siemens, Washington, USA) using 4–9 mHz and 5–13 mHz linear array transducers.

The evaluation criteria for gray-scale US included: size, echotexture, internal morphology, contour, presence of microcalcification, and the presence of a halo sign. The size of the nodule was defined as the largest size in any of the three dimensions, which were measured in transverse and longitudinal planes. Microcalcification was defined as hyperechoic spots below 2 mm with/without acoustic shadowing and without comet artifact. Internal morphology was categorized as solid, mixed, or cystic according to the ratio of solid and cystic components. A solid nodule was defined when a nodule had a cystic component, compromising less than 25% of it and a cystic nodule was defined when a nodule consisted of more than 75% cystic spaces. Echogenicity of the nodule was identified by comparing the nodule with the thyroid parenchyma and strap muscles, and qualified as hypoechoic, hyperechoic, and isoechoic. The contour of the nodule was categorized as well-defined or spiculated/irregular. The absence or discontinuity of a peripheral halo sign was evaluated.

On CDUS, vascular flow patterns were classified as Types I, II, III, and IV.

Type I: No visible flow

Type II: Peri-nodular (peripheral) flow

Type III: Peri-nodular flow (peripheral) with minimal internal flow

Type IV: Marked internal flow (intrinsic hypervascularity) or marked internal flow with peripheral flow. Marked internal flow was qualified as flow in the central part of the tumor greater than that in the surrounding thyroid parenchyma.

Resistive index (RI) was recorded, which was performed on one to three arteries of greater caliber in a vascularized nodule. Nodules consisting of central and peripheral flow, the measurements were taken in both vascular portions. Resistive Index was automatically calculated in the software, and for all nodules, average values were obtained.

Statistical analyses were performed using SPSS 11.5. Frequency (percent) for categorical variables, mean±standard deviation for metric variables was given as descriptive statistics. In order to compare two independent groups in terms of categorical and metric variables, the chi-square test and Mann-Whitney U-test were used, respectively. The area under receiver operating characteristics (ROC) curve was evaluated for the examination of diagnostic performance of RI. Additionally, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. $P<0.05$ was considered statistically significant.

Results

In this study, there were 48 (80%) benign and 12 (20%) malignant nodules. Out of 12 malignant nodules, 11 were papillary carcinomas, 1 was a follicular carcinoma. All malignant nodules were solitary. Overall nodule size ranged from 3 mm to 50 mm with a mean value 14.87±10.54 mm. Out of 60 nodules, 58 (96.7%) were solid and 2 (3.3%) were mixed morphology. All malignant nodules and 46 (95.8%) benign nodules had a solid appearance. None of the nodules were in cystic in nature. There were no statistically significant differences between benign and malignant nodules regarding size ($p=0.3$) and internal morphology ($p=1$).

Hypoechogenicity was a common gray-scale US feature in malignant nodules (91.7%), whereas for benign nodules, all three categorized echogenicity were seen. A total of 15 (31.3 %) of 48 benign nodules were hypoechoic, 19 (39.6%) nodules were isoechoic, and 14 (29.2%) nodules were hyperechoic. For echogenicity, statistically significant difference was found between benign and malignant nodules ($p=0.001$).

Of 12 malignant nodules, 11 nodules (91.7%) had an absent or discontinuous peripheral halo. Ten (83.3%) malignant nodules showed irregular contour, whereas irregular contour was detected in 3 (6.3%) out of 48 benign nodules. Microcalcifications were detected in 7 of 12 (58.3%) among the malignant nodules (Figure 1) and 4 of 48 (8.3%) among the benign nodules.

There was a statistically significant difference between benign and malignant nodules regarding the presence of microcalcifications, irregular contour, and the absence of a peripheral halo ($p<0.001$). Table 1 shows the distribution of the gray-scale ultrasonographic features related to the histology, which were found statistically significant for indicating malignant thyroid nodules in this study. The gray-scale US features of hypoechogenicity, irregular contour, presence of microcalcification, and the absence of a peripheral halo were more common in malignant nodules. Comparing the gray-scale US findings, the feature with the highest specificity and positive predictive value was irregular contour (93.8% and 76.9%, respectively). Table 2 shows the comparative intragroup analysis of gray-scale US features and CDUS features between benign and malignant nodules.

A great majority of malignant nodules had internal vascular flow. A total of 8 of 12 (66.7%) malignant nodules were categorized as Type IV in

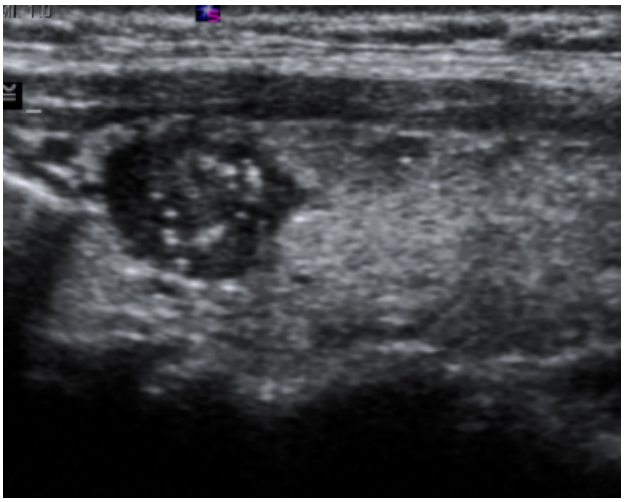

Figure 1. Microcalcifications in a hypoechoic thyroid nodule

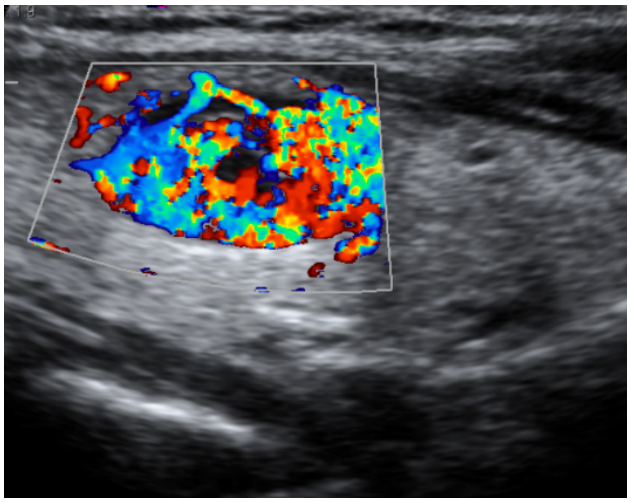

Figure 2. Type IV vascular flow pattern in papillary carcinoma with a pathological diagnosis of papillary carcinoma

Table 1: Gray-scale ultrasonographic features related to histology

	Echogenicity			Peripheral halo		Contour		Microcalsification		Total
	Hyperechoic	Isoechoic	Hypoechoic	Presence	Absence	Well-defined	Irregular	Presence	Absence	
Benign	14 (29.2%)	19 (39.6%)	15 (31.3%)	41 (85.4%)	7 (14.6%)	45 (93.8%)	3 (6.3%)	4 (8.3%)	44 (91.7%)	48
Malignant	1 (8.3%)	0 (0%)	11 (91.7%)	1 (8.3%)	11 (91.7%)	2 (16.7%)	10 (83.3%)	7 (58.3%)	5 (41.7%)	12

Table 2: Diagnostic data for gray-scale ultrasound and color Doppler ultrasound features of malignant nodules

	Malignant %	Benign %	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
Hypoechogenicity	91.7	31.3	91.6	68.7	42.3	97
Absence of peripheral halo	91.7	14.6	91.7	85.4	61.1	97.2
Irregular contour	83.3	6.3	83.3	93.8	76.9	95.7
Presence of microcalcification	58.3	8.3	58.3	91.7	63.6	89.8
Type IV flow pattern	66.7	16.7	66.7	83.3	50	90.9

Table 3: Distribution of the types of flow patterns among benign and malignant nodules

	Benign	Malignant	Total
Type I flow pattern	6 (12.5%)	0 (0%)	6 (10%)
Type II flow pattern	15 (31.3%)	0 (0%)	15 (25%)
Type III flow pattern	19 (39.6%)	4 (33.3%)	23 (38.3%)
Type IV flow pattern	8 (16.7%)	8 (66.7%)	16 (26.7%)
Total	48 (80%)	12 (20%)	60 (100%)

CDUS (Figure 2). In the current study, none of the malignant nodules showed Type I or Type II flow pattern. Table 3 shows the distribution of the types of flow patterns among benign and malignant nodules. Among the other types of flow pattern, Type IV presented highest specificity and sensitivity (83.3% and 66.7%, respectively) with a 50% positive predictive value and a 90.9% negative predictive value.

RI was significantly higher in malignant nodules (Figure 3). The mean value of RI was 0.80±0.15 (range: 0.50-1) in malignant nodules and 0.52±0.06 (range: 0.45-0.77) in benign nodules. Among the benign nodules, the highest RI (RI=0.77) was detected in follicular adenoma. The best results were calculated for a RI≥0.69 cut off value, with 91% sensitivity and 97% specificity in discriminating malignant nodules.

We also evaluated a combination of gray-scale US features and CDUS features for discriminating malignant nodules (Table 4). The absence of a peripheral halo, irregular contour, and Type IV flow pattern indicated the highest specificity (100%) and positive predictive value (100%) to predict malignancy with a 66.7% sensitivity and 92.3% negative predictive value.

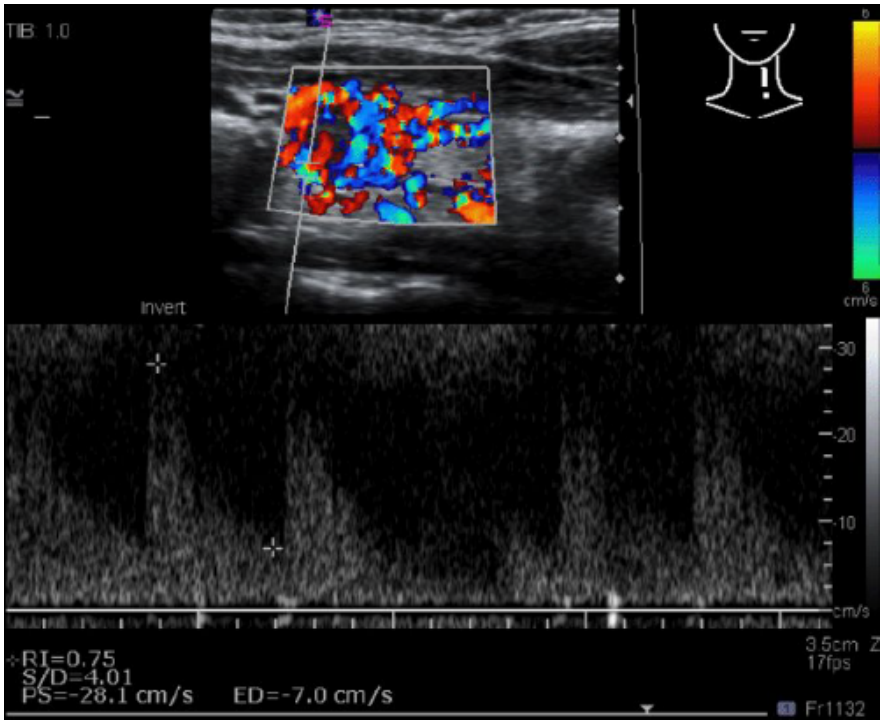

Figure 3. Spectral analysis of arterial vascularity shows a high resistance waveform with a RI value of 0.75. This nodule had a diagnosis of papillary carcinoma.

Discussion

Nodular thyroid disease is very common and a great majority of nodules are benign. Thyroid cancer prevalence ranges from 1.5% to 10% (12). Although thyroid malignancy is rare, it is important to discriminate malignant from benign nodules because it is one of the most curable malignancy. Furthermore, early and accurate diagnosis could alter the therapeutic approach (13). Thyroid US is the most prevalent method to detect and characterize the thyroid nodules. There are a great number of studies discussing the sonographic and Doppler findings for thyroid nodules in the literature, yet there is no common consensus. The current study demonstrated that the integration of CDUS and gray-scale ultrasound findings improved the specificity and positive predictive value in identifying malignant nodules.

In the current study, no statistically significant difference was found in predicting malignancy according to nodule size and morphology (p=0.3, p=1, respectively). Twelve (100%) malignant nodules and 46 (95.8%) benign nodules had a solid appearance. Likely for the benign nodules, the mean nodule size was 14.67±11.07 mm, and for the malignant nodules the mean nodule size was 15.68±8.4 mm. The results of the current study supported the findings in the literature. Previous researchers similarly declared that nodule size and internal morphology were not predictive of malignancy (14,18).

Table 4: Gray-scale ultrasound and color Doppler ultrasound combination features related to malignant histology in thyroid nodules

	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
Hypoechogenicity+ type IV flow pattern	66.7	93.8	72.7	91.8
Presence of microcalcification+ type IV flow pattern	41.7	97.9	83.3	87
Absence of peripheral halo +type IV flow pattern	66.7	93.8	72.7	91.8
Absence of peripheral halo+irregular contour+ type IV flow pattern	66.7	100	100	92.3
Absence of peripheral halo+ presence of microcalcification +type IV flow pattern	41.7	97.9	83.3	87
Hypoechogenicity + absence of peripheral halo +type IV flow pattern	66.7	93.8	72.7	91.8

Hypoechogenicity was a common gray-scale US feature in malignant nodules (12,18,19). In the current study, a total of 11 of 12 malignant nodules were hypoechoic. Benign nodules' echogenicities were variable. In this study hypoechogenicity is a valuable gray-scale US marker with a sensitivity of 91.6% and specificity of 68.7%. Hypoechogenicity was also frequently seen in benign nodules; therefore its specificity was the lowest in the gray-scale ultrasonographic criteria.

There was a statistically significant difference between benign and malignant nodules regarding the presence of microcalcifications ($p< 0.001$). Kim et al. (17) demonstrated that the presence of microcalcification is the most sensitive gray-scale US criteria in their study. Presence of microcalcification has a high specificity of 91.7%, which was the second highest specific finding in gray-scale US, sensitivity however was relatively lower compared to other findings that suggest malignancy such as contour abnormality and hypoechogenicity which may have resulted from lownumber of patients included in the study. Similarly, Moon et al. (12) declared that the presence of microcalcification can be considered as a highly specific finding for malignancy. The current findings are in concordance with their study.

In previous studies, a great majority of authors reported the association between the absence of a complete peripheral halo and malignancy (15,16,20,21). A peripheral halo is composed of compressed thyroid parenchyma and prominent vessels. In agreement with these reports, in the current study of 12 malignant nodules, 11 nodules (91.7%) had absent or discontinuous peripheral halo. An absent halo sign is the most sensitive parameter in the current study with a sensitivity of 91.7%, but it is less specific. In predicting malignancy with gray-scale ultrasound features, irregular/spiculated contour is the best single parameter with a specificity of 93.8%, sensitivity of 83.3%, positive predictive value of 76.9%, and negative predictive value of 95.7%.

CDUS examination has become a considerable imaging technique for discriminating malignant and benign thyroid nodules. Regarding CDUS findings, some vascular patterns were classified to differentiate benign and malignant nodules. In previous studies, many authors have shown the association between the increased intranodular blood flow and malignancy [3,9,19,22,23]. According to the data of the current study, increased intranodular blood flow (Type IV) was a statistically significant criterion to suggest malignancy ($p=0.001$). Tamsel et al. [24] and Algin et al. [25] did not find any relationship between high intranodular blood flow and malignancy .It is assumed that technical issues (settings of a wall filter and pulse repetition frequency) and patients lack of cooperation (breathing-swallowing motion artifacts) may have hidden the possible relationship between intranodular vascularity and malignancy in these studies.

In addition to vascular patterns, there are several studies that have shown the relationship with the histology of the thyroid nodules and vascular resistance [3,5,13,19,26]. RI is a good spectral Doppler parameter for evaluating thyroid nodules because it is not dependent on the angle of insonation. In the literature, many authors declared that RI values in malignant nodules were higher than in benign nodules [3,5,19,23,26]. Ivanac et al. [3] calculated the optimal cut-off value as $RI\geq0.70$ to distinguish malignant nodules from benign nodules with a sensitivity of 80% and specificity of 92%. De Nicola et al [5], Holden [19], and Cerbone et al. [13] reported similar results and found mean RI values for carcinomas of 0.75, 0.76, and 0.75, respectively. These studies suggested that large quantities of stenosis and occlusions in the neovascularization of differentiated thyroid carcinomas lead to an increase in vascular resistance. Similarly, in the current study, RI was significantly higher in malignant nodules (0.80 ± 0.15 vs. 0.52 ± 0.06) and $RI\geq0.69$ was highly suggestive of malignancy with a sensitivity of 91% and specificity of 97%. However, Tamsel et al. [24] reported poor sensitivity and specificity values of 11% and 4%, respectively, for an RI cut-off of 0.75. The study of Tamsel et al. [24] was based on cytological results acquired by FNAB. False negative results could arise in some cases, which might have potentially altered the results of this study.

In the literature, they also analyzed gray-scale US and CDUS features in combination and reported increased specificity by combining CDUS and US in the detection of malignancy in thyroid nodules [9,15,16]. In the current study with the combination parameters (Table 4), there was an improvement in specificity and positive predictive value. On the contrary, Stacul et al. [8] did not report an improvement in diagnostic performance of malignant thyroid nodules. This disagreement may be related, using the cytology as the reference standard, and therefore the results could be deviated. In the current study, among the associations of several US patterns with CDUS; the absence of a peripheral halo, irregular contour, and Type IV flow pattern is the most valuable combination with a specificitiy of 100%, sensitivity of 66.7%, positive predictive value of 100%, and negative predictive value of 92.3%.

There are some limitations in this study. Firstly, the number of the patients that were included in the study was limited. Secondly, a great majority of the malignant nodules were papillar carcinoma. Additional studies should be performed with a larger population including other types of thyroid malignancies. The strength of this study was that all nodules in this study had histological reports obtained from surgical specimens**.**

In conclusion, the results of present study indicate that CDUS gave an incremental value to gray-scale US in the diagnosis of malignant thyroid nodules. Due to the high specificity and positive predictive value, the findings of combined CDUS and gray-scale US features can determine malignant thyroid nodules and patients with such nodules may undergo surgery without the need of FNAB.

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