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# The Diagnostic Value of Color Doppler Ultrasonography in Predicting Thyroid Nodules Malignancy

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## Abstract

**Background and Objective:** Thyroid nodules are common medical and surgical problems. Although ultrasound has been proposed for evaluation of these nodules by many studies, but there is no consensus regarding its diagnostic accuracy and discriminatory cutoffs.

We aimed to investigate the diagnostic value of Gray-scale and Color Doppler US in predicting thyroid nodules malignancy.

**Method:** This is an analytical cross-sectional study which was conducted on 63 patients with thyroid nodules. The patients with nodular goiter were evaluated by Color Doppler and Gray scale US, fine needle aspiration and surgery was performed in all the subjects. The sensitivity, specificity, positive predictive value, and negative predictive value of the finding in US and their cut offs were calculated. Data were analyzed by Chi-square and Mann Whitney U test in SPSS19. P-value less than 0.05 considered as statistically significant.

**Results:** 63 patients consisting of 55 (87.3%) female and 8 (12.7%) male patients with the age range of 20-70 years were enrolled in this study. 14% of nodules were reported as malignant in pathology. Singularity, hypo echogenicity, irregular margin, and micro calcification were significantly correlated with malignancy in nodules ($p<0.05$). Micro calcification and hypo echogenicity of the nodule were the most and the least discriminator of malignancy in nodules (sensitivity 77%, specificity 76% *vs.* 24%, PPV 41% *vs.*, 14% and NPV 94% *vs.* 86%) respectively.

Pulsatility Index and Mean Systolic Velocity were the most and the least predictor factors of thyroid malignancy (PPV 62% *vs.* 23% and NPV 100% *vs.* 91%, respectively). There was a significant association between Resistive Index and Pulsatility Index with malignancy with a cutoff of $RI \geq 0.715$ ($P=0.005$) and $PI \geq 0.945$ ($P=0.007$), respectively. The combination of calcification, $RI \geq 0.715$ with $PI \geq 0.945$ had a very diagnostic yield for diagnose of malignancy (PPV 66.6% and NPV 98.4%).

**Conclusion:** According to results, it seems that Grayscale US combined with Color Doppler are valuable modalities for evaluating thyroid nodules and can be used as a para-clinical method in order to assess the risk of malignancy in the patient with thyroid nodules.

**Keywords:** color doppler, ultrasonography, thyroid nodule, neoplasms.

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## INTRODUCTION

Thyroid nodules are common medical and surgical problems[1].They can be evaluated by many techniques including physical examination, fine needle aspiration, and imaging[2]. Even though thyroid malignancy may be detected in 5% of thyroid nodules, early diagnosis and treatment are recommended because of nodules' slow progress and long survival[3,4].

The American Thyroid Association endorses performance of ultrasonography (US) in all thyroid nodules because it is a safe, low cost modality with lack of ionizing radiation, and with no harm to the body tissues[5]. Ultrasonography as a routine method of thyroid evaluation is an effective mean for discovering intangible nodules and a guide for biopsy of suspicious ones[6]. Gray-scale US reports features of nodules, such as texture, echogenity, number, margin and calcification. Color Doppler is a technique that has been mentioned as a proper modality for diagnosing benign and malignant lesions. It can carefully evaluate nodular and perinodular blood flows[7,8].

Many studies focused on the effect of US as valuable tool for detecting benign and malignant lesions and different guidelines were proposed[5,9]. But there is no consensus on its' usage and diverse cutoffs have been proposed. Therefore, according to controversial results regarding its usefulness in diagnosing thyroid malignancy, we aimed to investigate the diagnostic value of Color Doppler US in predicting thyroid nodules malignancy[8,10-16].

## METHODOLOGY

### Patients

This is an analytical cross-sectional study, which was conducted on 63 patients with thyroid nodules referred to an endocrinology clinic in Rasht (a metropolitan at the Caspian coast). The inclusion criteria were the presence of thyroid nodules and the indication for surgery because of suspicious and/or indeterminate fine-needle biopsy (FNA-B) and/or clinical risk factors for thyroid nodules. The study was carried out according to the principles of the Declaration of Helsinki, and informed written consent was obtained from all the patients.

### Data gathering

Data were collected by a check list consisted of demographic characteristics, the results of color Doppler and gray scale US and pathologic findings. Consent letter was obtained before enrolment.

Color Doppler and Gray scale US were performed separately by the same radiologist before surgery. The B-K medical 2009 US with high frequency (6-14 MHz) transducers was used. It allows detecting small nodules with 2-3 mm in diameter.

Surgery is the gold standard for diagnosing malignancy of thyroid nodules, US results were compared with the surgical pathologic findings.

Gray Scale US assessed lesion's features including number of nodules (solitary and multiple), echogenity (hypo echoic, isoechoic and hyper echoic), texture (homogeneous and heterogeneous), margin (irregular and regular margin), calcification (micro calcification and coarse calcification), type (solid or cystic) and the existence of halo.

Color Doppler evaluated the vascular status of nodules (intranodular or perinodular vessels), Resistive Index (RI), Pulsatility Index (PI), and Mean Systolic Velocity (MSV). Peak Systolic Velocity (PSV) and End Diastolic Velocity (EDV) were measured and RI and PI were calculated by the following formulas.

RI = (PSV-EDV)/PSV.

PI = (PSV-EDV)/MSV.

After collecting FNA and US results, the eligible patients had a thyroid surgery performed and the nodular tissue was assessed pathologically.

### Statistical analysis:

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of US were calculated. Also, the accuracy of the RI, PI, and MSV and their optimal cut-off points were evaluated by the receiver operating characteristic (ROC) curve. Data were analyzed by chi-square and Mann Whitney U test in SPSS 19.95% confidence interval was noted and P-value less than 0.05 considered as statistically significant.

## RESULTS AND DISCUSSION

63 patients consisting of 55 (87.3%) female and 8 (12.7%) male patients with the age range of 20-70 years enrolled in this study. Pathologic finding mentioned 9 (14%) malignant nodules.

The rate of malignancy in single and multiple nodules was 11 out of 16 and 4 out of 47 respectively. Among 17 hypo echoic nodules, 6 were malignant. As well 3 of 7 nodules with irregular border, 7 out of 17 nodules with micro calcification and 8 of 13 solid nodules were reported as malignant in pathology. In Gray scale ultrasonography singularity, hypo echogenicity, irregular margin, and micro calcification were significantly correlated with malignancy in nodules ($p<0.05$). Irregularity of the nodular border had the least sensitivity (33%), and micro calcification and heterogeneity had the most sensitivity (77%) for diagnosis of thyroid malignancy. Irregularity of the nodular boarder and hypo echogenicity had the most and the least specificity (92% *vs.* 24% respectively).

Micro calcification and hypo echoic texture of the node were the most and the least predicting factors of malignancy in nodules (sensitivity 77%, specificity 76% vs. 24%, PPV 41% vs.14% and NPV 94% vs.86%)

respectively. Table 1 summarizes the features of Gray scale US with their sensitivity, specificity, PPV and NPV.

In color Doppler ultrasonography Pulsatility Index and Mean Systolic Velocity were the most and the least discriminator of thyroid malignancy (PPV 62% *vs.* 23% and NPV 100% *vs.* 91% respectively). The pattern of nodular blood flow (intra and perinodular) and Mean Systolic Velocity were not discriminatory between benign and malignant nodules. There was a significant association between Resistive Index and Pulsatility Index with malignancy with a cutoff of RI ≥ 0.715 (P=0.005) and PI ≥ 0.945 (P = 0.007) respectively (Table 2). The combination of the three factors in gray scale and Doppler US with the highest sensitivity and specificity (>70%) showed that combining calcification, RI ≥ 0.715 with PI ≥ 0.945 had a very diagnostic yield for diagnose of malignancy (PPV 66.6% and NPV 98.4%) (Table 3).

Our results showed that 87% of patients with nodular diseases were female which was consistent with Fukunari et al. study, reporting that 85% of patients with nodular diseases were female (13)and other epidemiologic studies indicating the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world[13,17,18].

The prevalence of thyroid cancer had been shown to be 5-15% in different studies[19,20]. In our study, 14% of nodules were malignant. While Jason et al. study on 80 patients reported a rate of 5.33% malignancy in their study population and a Turkish study on 169 nodules mentioned a rate of 6% malignancy in their patients[11,21].

Algin et al. prospectively examined 77 thyroid nodules in 60 patients and observed a significant relationship between malignancy and irregular margins, micro calcifications, and hypo echogenicity on Gray scale ultrasound examination (p<0.05). They also determined vascularity by Doppler US. Imaging was defined as

**Table 1.** Gray scale and color doppler US findings.

| Features of lesions | Malignant | Benign | P-value* (C.I.) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| **Multiciplity** | | | | | | | |
| Solitary | 5 | 11 | P = 0.025 (1.2-12) | 55 | 79 | 31 | 91 |
| Multiple | 4 | 43 | | | | | |
| **Echogenity** | | | | | | | |
| Hypo echoic | 6 | 11 | P = 0.004 (1.5-19) | 66 | 79 | 35 | 93 |
| Iso echoic & hyper echoic | 3 | 43 | | | | | |
| **Texture** | | | | | | | |
| Heterogeneity | 7 | 41 | P = 0.9 (0.2-4.7) | 77 | 24 | 14 | 86 |
| Homogeneity | 2 | 13 | | | | | |
| **Margin** | | | | | | | |
| Irregular border | 3 | 4 | P = 0.02 (1.2-12) | 33 | 92 | 42 | 89 |
| Regular border | 6 | 50 | | | | | |
| **Calcification** | | | | | | | |
| Micro calcification | 7 | 10 | P = 0.02 (0.3-0.8) | 77 | 76 | 41 | 94 |
| coarse calcification | 2 | 44 | | | | | |
| **Types** | | | | | | | |
| Solid | 5 | 8 | P = 0.012 | 55 | 79 | 31 | 91 |
| Cystic | 4 | 46 | | | | | |
| **Halo** | | | | | | | |
| Absent | 7 | 35 | P = 0.445 (0.3-07) | 44 | 35 | 10 | 79 |
| Present | 2 | 19 | | | | | |
| **Intra and peri nodular vascularity** | | | | | | | |
| Present | 7 | 28 | P = 0.14 (0.6-12) | 77 | 48 | 20 | 92 |
| Absent | 2 | 26 | | | | | |

*Chi-square

**Table 2.** The calculated "cut off points" for RI, PI and MSV for the prediction of malignancy in thyroid nodules.

| | Cut off Point (≥) | Mean | P-value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Resistive Index (RI) | 0.715 | 0.6 | 0.005 | 88.9 | 79 | 42 | 97 |
| Pulsatility Index (PI) | 0.945 | 0.78 | 0.007 | 100 | 90 | 62 | 100 |
| Mean Systolic Velocity (MSV) | 33.5 m/s | 34 m/s | 0.349 | 66 | 62 | 23 | 91 |

**Table 3.** The calculated diagnostic value of combined characteristics.

| Features of lesions | Malignant | Benign | P-value* (C.I.) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| **Combined characteristics** | | | | | | | |
| Yes | 8 | 4 | P = 0.001 | 88.88 | 92.6 | 66.66 | 98.04 |
| No | 1 | 50 | | | | | |

non-vascular, peripheral, central, or of mixed type. They reported that vascularity was not a useful parameter for distinguishing malignant from benign thyroid nodules in their study group [22]. In a study retrospectively analyzing the sonographic features of 34 malignant and 36 benign thyroid nodules with respect to size, echogenicity, echo structure, shape, border, calcification, and internal vascularity, intrinsic calcification was the only statistically significant predictor of malignancy (35.3% sensitive and 94.4% specific; P<0.005). Presence of a "snowstorm" pattern of calcification was 100% specific for malignancy. Echogenicity, echo structure, shape, border classification, and grade of internal vascularity with various combinations of these features did not show any significant difference between benign and malignant nodules in this study[11].

In another study on thyroid nodules with diameter of 15 mm and smaller, the most reliable diagnostic criteria for malignancy were irregular outline (sensitivity, 69.6%; specificity, 86.4%; P<0.001), sub capsular location (sensitivity, 65.2%; specificity, 86.4%; P<0.001), and increased intranodular vascularization (sensitivity, 69.6%; specificity, 87.9%; P<0.01). They concluded that irregular tumor outline, sub capsular location, and increased intranodular vascularization in US were the most helpful findings in the diagnosis of thyroid malignancy in thyroid nodules with diameter of 15 mm and smaller[8].

In a study seventy eight consecutive patients with 78 thyroid nodules (29 single nodules and 49 nodular goiter) were examined by Doppler US, before surgery, evaluating the hypo echogenicity of the nodule, the presence of micro calcifications and the halo sign absence and the vascular pattern, which had been classified as follows: absence of blood flow (type I), perinodular blood flow (type II), intranodular, with or without perinodular blood flow (type III), which is considered the most typical pattern of malignancy. They reported that the micro calcification (P<0.0001, specificity 93%, sensitivity 59%); hypo echogenicity" (P < 0.0001, specificity 86%, sensitivity 73%), absent halo sign (P<0.0001, specificity 71%, sensitivity 82%), type IIIa pattern (intranodular without perinodular blood flow) were the most predictors of malignancy (P<0.0001, specificity 100%, sensitivity 36%), and their combination was the most specific for malignancy (P < 0.0001, specificity 96%, sensitivity 50%)[23]. In contrast in the present study the combination of the three factors in gray scale and Doppler US with the highest sensitivity and specificity (>70%) showed that combining calcification, RI ≥ 0.715 with PI ≥ 0.945 had a very diagnostic yield for diagnose of malignancy (Sensitivity 88.88%, Specificity 92.6%, PPV 66.6% and NPV 98.4% ).

Our results depicted that the existence of Hypo echogenic and solitary nodules with irregular margins and micro calcifications increased the probability of malignancies. This is in agreement with previous studies mentioning that solitary nodules, hypoechogenicity, irregular and lobulated margin, and micro calcification were significantly associated with malignancy[8,13,21,23].

Nodule vascularity has also been proposed to be of diagnostic value, but many authors question this proposal. There is no consensus which type of vascularity would be considered suspicious of malignancy[11,16,21,24-26].

Some scientific organization considers “increased intranodal vascularity” as suspicious, without requiring that vascularity is predominantly or exclusively intranodal. Others scientific societies propose only “predominantly or exclusively central” blood flow to be defined as suspicious[5,9,27-29].

We found no significant difference between intranodular and perinodular blood flow and vascularity as whole in the benign and malignant nodules in Color Doppler sonography. Our findings were consistent with Summaria et al., Rago et al. and Tamsela et al. and in contrast with previous Iranian and Japanese studies reporting a direct relationship between high intranodular vascularity with the probability of nodule malignancy[13,21,23,26,30].

A prospective study on 169 thyroid nodules in 134 patients indicated that Doppler US characteristics, including vascular pattern, RI and MSV were not useful parameters for distinguishing malignant from benign thyroid nodules and they could not be used as a diagnostic method to determine which nodules should undergo FNAB. Tamsela et al. reported no significant association between intranodular RI = 0.49 and malignancy. They did not determine the sensitivity, specificity, PPV, and NPV[21].

In contrast, Bakhshaee et al mentioned significant relationship between RI = 0.68 and malignancy. Algin et al. also illustrated that RI (cutoff>0.71) and PI (cutoff>0.97) values were useful in distinguishing malignant from benign thyroid nodules[22,30]. In the present study we showed significant relationship between Resistive Index ≥ 0.715 and malignancy with sensitivity, specificity, PPV and NPV of 88.9%, 79%, 42% and 97% respectively for detecting malignant nodules.

A Japanese study mentioned significant relationship between PI cut off point of 1.01 and malignancy of nodules (specificity of 79.0% and sensitivity of 69.1%)[13].

In our study, there was a notable relation between Pulsatility Index (p = 0.007) and malignancy in thyroid nodules with a cutoff value of 0.945 and a sensitivity, specificity, PPV, and NPV of 100%, 90%, 64% and 100% respectively for detecting malignant nodules.

In our study group, the estimated ROC curve areas for MSV was 33.5 cm/s which showed no significant difference between the benign and malignant nodules. Our findings were consistent with previous Turkish investigation. They mentioned that MSV with a cut off of 49 cm/s had no significant relationship with malignancy of nodules but in multivariate logistic regression analysis, they noted micro calcification and PI to be significantly related with malignancy[21].

## CONCLUSION

According to results, it seems that Gray scale combined with Color Doppler US are valuable modalities for evaluating thyroid nodules and can be used as a Para-clinical method in order to assess the risk of malignancy in the patient with thyroid nodules.

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