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DIAGNOSTIC VALUE OF DUPLEX DOPPLER ULTRASOUND PARAMETERS IN PAPILLARY THYROID CARCINOMA

A. Aslan[1,*], S. Sancak[4], M. Aslan[1], E. Ayaz[1], I. Inan[1], S.S. Ozkanli[2], O. Alimoğlu[3], A. Yıkılmaz[1]

Medical School of Istanbul Medeniyet University, Göztepe Training and Research Hospital, [1]Dept. of Radiology, [2]Dept. of Pathology, [3]Dept. of General Surgery, [4]Fatih Sultan Mehmet Training and Research Hospital, Dept. of Endocrinology, Istanbul, Turkey

Abstract

Context. Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer due to its high fibrotic content; it can affect the blood flow resistance.

Objective. To introduce duplex Doppler ultrasonography (DDUS) parameters of papillary thyroid carcinoma (PTC) and their correlation with size.

Design. The study was designed as a prospective study.

Subjects and Methods. Thyroid nodules of the patients who were already scheduled for thyroid surgery either for malignant thyroid nodules or multinodular goiter were evaluated for DDUS parameters. Size, systolic to diastolic flow velocity (S/D) ratio, pulsatility index (PI), and resistive index (RI) of each nodule were recorded. Nodules were diagnosed as PTC or benign nodules based on histopathology. DDUS parameters were compared between PTCs *versus* benign nodules and micro PTCs (≤ 10 mm) *versus* large PTCs (> 10 mm). A correlation analysis was performed between the size and DDUS parameters.

Results. 140 thyroid nodules (30 PTCs, 110 benign nodules) were obtained. The mean S/D ratio, PI, and RI values were significantly higher in PTC than in benign nodules (p values were 0.0001, 0.0003, and 0.0001 respectively). The optimal cut-off values of S/D (0.732), PI (0.732), and RI (0.738) had accuracy rates of 71%, 69%, and 69%, respectively. There was no statistically significant difference between micro PTC and large PTC with regards to DDUS parameters. The size and DDUS parameters of PTC showed no significant correlation.

Conclusions. PTC has a high resistive flow pattern regardless of its size; however the clinical utility of DDUS to differentiate a PTC from benign nodule is limited.

Key words: Papillary thyroid carcinoma, Duplex Doppler ultrasonography, Thyroid nodule, Vascular resistance.

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma with a good prognosis (1-4). Gray-scale ultrasonography (US) is the primary method for predicting the malignant potential of a thyroid nodule that should undergo fine needle aspiration biopsy (FNAB). However, there is no single US criterion (5-7).

Color Doppler US (CDUS) is a widely available diagnostic tool; nevertheless, it is subjective and has no reliable outcomes for predicting PTC (8-11). Spectral duplex Doppler US (DDUS) parameters are more objective than CDUS and have been claimed to have a role in detecting PTC. However, different studies produced controversial results and sustained the debate about whether PTC can be diagnosed using DDUS parameters (12-16). In this study, we hypothesized that DDUS parameters of PTC could be used for differentiating PTC from a benign nodule and conducted a prospective study. Different from the previous reports the histopathological diagnoses of the nodules were obtained. Also, we evaluated the DDUS parameters of papillary micro thyroid carcinoma (≤ 10 mm) (PMTC) and large PTC (> 10 mm) to determine any possible relationship.

MATERIALS AND METHODS

This prospective study had approval from the institutional research ethics board, and a written informed consent form was obtained from all patients.

Patients

All consecutive patients scheduled for subtotal or total thyroidectomies due to multinodular goiter, or malignant or suspicious FNAB results were

*Correspondence to: Ahmet Aslan, Medical School of Istanbul Medeniyet University, Dept. of Radiology, Istanbul, 34620, Turkey, E-mail: aslahmet@gmail.com

within the scope of the study. The inclusion criteria were as follows: (1) scheduled for subtotal or total thyroidectomy, (2) having nodular thyroid disease confirmed by the gray-scale US, (3) cooperated with DDUS evaluation and (4) had a histopathological diagnosis of PTC or benign nodule. The exclusion criteria were: (1) patients who could not cooperate with the operator during the DDUS examination, (2) nodules that were intertwined or difficult to depict on their own, (3) nodules without vascularity on CDUS, (4) nodule without histopathological diagnosis or (5) malignant thyroid nodule other than PTC. Patients who met the inclusion and exclusion criteria underwent DDUS. All nodules in multinodular goiter were evaluated separately for statistical analysis.

Equipment and Scanning Procedures

US and DDUS studies were performed with diagnostic US scanners (Toshiba Aplio 500, Toshiba Medical Systems, Tokyo, Japan; HI VISION Preirus, Hitachi Medical Corporation, Tokyo, Japan) using a multi-frequency linear array probe within a week before the surgery. During DDUS and US, patient's head was in hyperextension in the supine position and the patient was asked to hold his breath and not to swallow. A single observer with a 10 years experience in US performed the US and CDUS studies without knowledge of the patients' information or history. The location (right or left lobe and isthmus) and size of the nodule (mm- maximum size in any plane), patient's age (years) and gender were noted. Nodule location in the thyroid gland was described in three axes (inferior or superior, anterior or posterior, and medial or lateral). DDUS was performed on arteries either along the periphery or at the center of each nodule with appropriate sample volume, wall filter settings, and pulse repetition frequency (Fig. a, b). The sampled vessel was selected if it had arterial flow pattern and had enough caliber to set an appropriate sample volume. DDUS was done gently to prevent compression of the vascular structures by the US probe.

A minimum of three spectral waveforms were obtained for each nodule, and the mean values of the two waveform analyses were used to assess the systolic/diastolic flow velocity (S/D) ratio, pulsatility (PI) and resistive indexes (RI). The spectral waveform tracing and the DDUS parameter calculations were done automatically by the US machine (Fig. b).

Surgical Procedures

Total or subtotal thyroidectomy procedures were chosen by the thyroid surgeons as convenient treatment options. Additionally, cervical lymph nodes were excised in patients with suspicious FNAB results.

Histopathological Analysis

A single observer correlated and confirmed the locations of the nodules in the surgical specimens with US findings to be sure for the final diagnosis. An expert pathologist classified all nodules according to World Health Organization criteria (17). The final histopathological results of the study included PTC, follicular adenoma (FA), colloid nodule and nodular hyperplasia.

Statistical Analysis

For the statistical analysis, thyroid nodules were grouped into two categories as PTC *versus* benign nodule (FA, colloid nodule, and nodular hyperplasia), and PTMC *versus* large PTC.

A commercially available statistics program (MedCalc Statistical Software, version 12.7.7, MedCalc Software bvba, Ostend, Belgium, 2013) was used to analyze the collected data, and Shapiro-Wilks

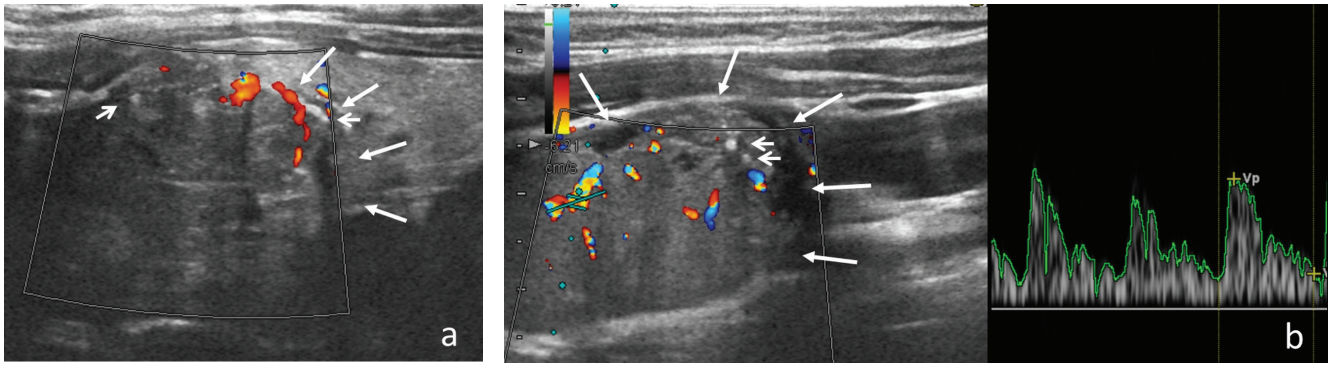


Figure a,b. A 33-year old female patient with a 25 mm sized, right lobe sided, a hypoechoic nodule that contained irregular margins (long arrows) and microcalcifications (short arrows). The nodule had a small amount of peripheral vascularization on the color Doppler US (a). The S/D ratio, PI, and RI values were 3.69, 1.28, and 0.73, respectively (not shown) (b). The histopathologic evaluation confirmed the diagnosis of papillary thyroid carcinoma.

test was used to investigate the normality of continuous variables. Continuous variables were presented using mean (± SD) for normally distributed variables and median (range values) for non-normally distributed variables. Student's T-test and Mann-Whitney U test were used for comparing continuous variables. Receiver operating characteristic (ROC) curve analysis and Youden's index were used to obtain threshold values to predict PTC for statistically significant spectral DDUS parameters. Pearson correlation analysis was performed to display correlations between PTC size and the S/D ratio, PI and RI values. A correlation coefficient was considered low if the coefficient value (r) was between 0 – 0.3, moderate if the coefficient value was between 0.3 – 0.5, and high if the coefficient value was between 0.5 – 1.0. Statistical significance was accepted when the two-sided p value was lower than 0.05.

RESULTS

One hundred and nineteen consecutive patients scheduled for thyroid surgery were included in the study. Three patients with follicular carcinoma, 10 patients with multinodular goiter in which the nodule could not be depicted, 15 patients who did not fulfill the DDUS examination instructions, and 5 patients with nodules that were too small (< 5 mm) to detect vascularity on CDUS were excluded from the study. The final study group was composed of 140 nodules from 86 patients [69 (80.2%) female and 17 (19.8%) male]. Surgery was carried out in 39 patients due to suspicious or malignant FNAB results and in 47 patients due to cosmetic reasons (swelling or mass feeling in the neck) or symptoms of tracheal and esophageal compression such as shortness of breath, difficulty in swallowing or breathing, coughing, or hoarseness. Three patients had five thyroid nodules, four patients had four nodules, nine patients had three nodules, 12 patients had two nodules, and 58 patients had one nodule.

The histopathological diagnoses yielded PTC in 30 nodules, FA in 15 nodules, colloidal nodules in 15 patients and nodular hyperplasia in 80 nodules. The median sizes of PTC and benign nodules were 15 (range 6.2 – 47) mm and 26 (range 5.6 – 68) mm, respectively (Table 1). Spectral waveform analyses demonstrated that PTC had statistically significant higher S/D ratio, PI and RI values (p values were 0.0001, 0.0003, and 0.0001, respectively) (Table 1). ROC analysis was performed and Youden's index obtained optimal threshold values of > 3.11, > 0.92 and > 0.68 for S/D ratio, PI, and RI, respectively. The diagnostic performance of the spectral waveform parameters is presented in Table 2.

There were 9 PTMCs and 21 large PTCs. The median size of the PMTCs was 9.7 (range 6.2 - 10) mm, and the mean size

Table 1. The demographic and spectral duplex Doppler ultrasonography parameters of the groups

	Benign Nodule (n = 110)	Papillary Thyroid Carcinoma (n = 30)	Papillary Micro Thyroid Carcinoma (n = 9)	Large Papillary Thyroid Carcinoma (n = 21)	P*	P**
Gender (Female / Male)	90/20	27/3	9/-	18/3	0.407 [a]	0.261 [a]
Age (year)	46.50 (20 – 70)[b]	4.50 (9 – 68)[b]	46 (23 -54)[b]	41 (9 – 68)[b]	0.173 [c]	0.650 [c]
Size (mm)	26 (5.6 – 68)[b]	15 (6.2 – 47)[b]	9.7 (6.2 -10)[b]	20 (11 – 47)[b]	*0.002* [c]	*< 0.001* [c]
Systolic / Diastolic Ratio	2.48 (1.39–23.18)[b]	3.27 (1.83 – 9.56)[b]	2.79 (1.83 – 9.38)[b]	3.38 (2.19 – 9.56)[b]	*0.0001*[c]	0.316 [c]
Pulsatility Index	0.9 (0.36 – 2.36) [b]	1.13 (0.6 – 2.39)[b]	0.99 (0.6 – 2.39)[b]	1.19 (0.75 – 1.89)[b]	*0.0003*[c]	0.341[c]
Resistive Index	0.59 ± 0.11[d]	0.7 ± 0.11[d]	0.64 (0.45 – 0.89)[b]	0.7 (0.54 – 0.9)[b]	*0.0001* [e]	0.316 [c]

*Comparison between papillary thyroid carcinoma and benign nodules, **Comparison between micro and large papillary thyroid carcinoma.
a Fischer's Exact Test, b median (minimum – maximum) value, c Mann-Whitney U Test, d mean value ± standard deviation, e Student T-Test.

Table 2. The ROC analysis and estimated threshold values of spectral DDUS parameters

	Systolic / Diastolic Ratio	Pulsatility Index	Resistive Index
Az (95% CI)	0.732 (0.650 - 0.804)	0.724 (0.641 - 0.796)	0.738 (0.656 - 0.809)
p value	< 0.0001	0.0001	< 0.0001
Threshold value	> 3.11	> 0.92	> 0.68
Sensitivity (95% CI)	59.3 (38.8 - 77.6)	81.5 (61.9 - 93.7)	55.6 (35.3 - 74.5)
Specificity (95% CI)	82.7 (74.3 - 89.3)	55.5 (45.7 - 64.9)	82.7 (74.3 - 89.3)
PPV (95% CI)	77.4 (66.89 - 85.35)	64.6 (55.98 - 72.45)	76.3 (65.35 - 84.58)
NPV (95% CI)	67 (58.30 - 74.67)	75 (64.02 - 83.43)	65.1 (56.43 - 72.79)
Accuracy (%)	71	69	69

Abbreviations: ROC; receiver operating characteristic, DDUS; Duplex Doppler ultrasonography, Az; Area under the curve, CI; Confidence interval, PPV; Positive predictive value, NPV; Negative predictive value.

of large PTCs was 20 (range 11 – 47)mm. Differences in the S/D ratio, PI and RI values of PTMCs and large PTCs were statistically insignificant (p values were 0.316, 0.341, and 0.316, respectively) (Table 1). There were weakly positive but insignificant correlations between the size and S/D ratio, PI and RI values of PTC (r values were 0.134, 0.139 and 0.114, respectively, and p values were 0.504, 0.489 and 0.570, respectively).

DISCUSSION

Papillary thyroid carcinoma is a common thyroid malignancy representing 80% to 85% of all thyroid carcinomas (4). Histopathological findings have shown higher vascularization in PTC than benign thyroid nodules (2). Nevertheless, advances in CDUS technology have limited capacity in displaying the vascularity of PTC (2,8-11,18). On the other hand, the depiction of intranodular vascularization is not a predictive risk factor for PTC (8,11). However, spectral DDUS parameters can have a role in the differentiation of PTC from benign nodules. In our study, we showed that PTC had high resistive blood flow irrelevant to its size.

Ultrasonography is the primary imaging method for predicting the malignant potential of thyroid nodules. Microcalcification, hypoechogenicity, infiltrated or irregular margin, extrathyroidal extension, and taller rather than wide criteria are considered to be high-risk factors for PTC on US (3-6,19,20). However, no single US criterion can predict the malignant potential of a thyroid nodule alone. Additionally, these criteria are subjective and may vary according to the experience of the sonographer (2-4,21). Nodule vascularization was evaluated formerly by CDUS to improve the diagnostic performance of US, but results were conflicting and this is no longer accepted as a risk factor (2,7-12,18,20,21). Therefore, other imaging methods, such as elastography and contrast-enhanced US (CEUS), are used to select the nodule that requires FNAB. However, the utility of both methods in clinical practice remains restricted since they are operator dependent with unstandardised measurements, have limited accessibility, a need for advanced US probes with additional software, and the incremental cost of contrast medium (22-25).

The S/D ratio, PI, and RI values are objective and can easily be measured without concern for the Doppler angle, the course of the artery or sample volume placement (5,8,17,26-28). Thus, DDUS can be performed by all sonographers, regardless of their individual experience. Many authors have concluded that an RI value > 0.70 and a PI value > 1.0 are related to thyroid malignancies. However, most of these studies compared benign and malignant nodules and used FNAB as a reference test, producing overlaps and conflicting results (5,8,9,27,28). We compared the spectral DDUS parameters of histopathologically proven nodules and used gray-scale US images to locate the nodules in thyroidectomy materials, different from previous studies. The S/D ratio, PI, and RI values were all significantly higher in PTC than benign nodules, but not significantly different between PMTC and large PTC. The increase in cellularity, the presence of fibrosis, and newly formed disorganized vessels are likely to result in fistula, stenosis, and occlusion that can lead to increased vascular resistance in PTC (5,9,18). In the current study, we found that an S/D ratio of > 3.11, a PI value of > 0.92 and an RI > 0.68 could differentiate PTC from benign nodules. However, the sensitivity and specificity values were not high enough and the accuracy of the S/D ratio, PI, and RI values ranged from 69% to 71%. Also, DDUS has some limitations such as longer scanning time and more effort to measure the DDUS parameters for each nodule. Thus, DDUS may be used as a complementary method to the gray-scale US in predicting PTC or selecting a nodule that should undergo FNAB.

PMTC (size ≤ 10 mm) has an indolent course and active surveillance with close US follow-up is recommended (18). The prognosis is dependent on the age, US findings and extrathyroidal extension (18, 29). Independent predictors of malignancy for PMTC are having infiltrative or irregular margins and being taller rather than wide in size (19). However, the cellular architecture of PMTC and large PTC are the same and there are no differences observed in the histopathologic specimens. Increasing size may improve the detectability of US characteristics, however, it may also alter the color and spectral DDUS features by compressing abnormal vessels or augmenting the flow volume (11, 20, 30). Thus, resistivity is expected to be lower in PMTCs compared to large PTCs on DDUS. We found higher S/D ratio, PI and RI values in large PTCs, as we expected, but they were not statistically significant. We also found weak, but insignificant correlations between spectral Doppler parameters and PTC size. These findings may be related to the fact that we performed spectral DDUS measurements on vessels at the periphery or center of the nodule. Algin *et al.* (5) found that mean PI and RI values obtained in the center

of benign and malignant nodules were higher than that obtained at the periphery of nodules. However, they did not compare their results. Similar to our findings, Zhou *et al.* (18) found weak and insignificant correlations between the size and PI - RI values of malignant and benign thyroid nodules. In this study, we could not apply DDUS parameters to the nodules that were smaller than 5 mm, as the smallest nodule which we could obtain the DDUS parameters was measured 5.6 mm. Similar to our study, previous studies comparing DDUS parameters in thyroid nodules did not include nodules smaller than 5 mm either (5,8,14-16,27,28). Therefore, DDUS parameters may have a role in predicting PTC if the lesion is greater than 5 mm.

This study had a few limitations. Firstly, the gray-scale US findings of the nodules were not evaluated. Secondly, the number of nodules that were included in this study was relatively limited hence only patients who underwent surgery were included in the study to reach a reliable diagnosis. Thirdly, there were no comparisons between the DDUS parameters of PTCs and other malignant thyroid nodules, such as medullary carcinomas, follicular carcinomas, anaplastic carcinomas, and metastases, due to their low incidence. Finally, it is possible that there might be a selection bias as we were unable to perform spectral DDUS of nodules smaller than 5 mm. However, this limitation seems to be related to the technology of US equipment.

In conclusion, PTC has high resistive flow pattern regardless of the size, however, the diagnostic performance of DDUS parameters to differentiate a PTC from a benign nodule is unsatisfactory.

Conflict of interest

The authors declare that they have no conflict of interest.

Conflict of interest

The authors declare that they have no conflict of interest. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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