Diagnostic value of 3D power Doppler ultrasound in the characterization of thyroid nodules

Abstract

Background/aim: To evaluate the diagnostic value of vascular indices obtained using 3D power Doppler ultrasound (3DPDUS) in differentiation of benign and malignant thyroid nodules.

Materials and methods: Sixty-seven patients (56 female, 11 male, mean age 44.6) with 81 thyroid nodules exhibiting mixed (peripheral and central) vascularization patterns and with the largest diameter of between 10 mm and 30 mm were prospectively evaluated using 3DPDUS. Nodule volume, vascularization index (VI), flow index (FI) and vascularization flow index (VFI) were calculated using Virtual Organ Computer-aided Analysis (VOCAL) software, and these indices were then compared with regard to the cyto-histopathology-based diagnosis. The optimum cutoff values for the differentiation of benign and malignant nodules were identified, and diagnostic efficacy was calculated using receiver operating characteristic (ROC) analysis.

Results: Fifty-six of the 81 nodules included in this study were diagnosed as benign and 25 as malignant. Vascular indices in malignant nodules were significantly higher than those in benign nodules (p<0.05). In benign nodules, mean VI was 11.61 ± 6.88, mean FI was 39.75 ± 3.93 and VFI was 4.82 ± 2.94, compared to 18.64 ± 12.81, 41.82 ± 4.43 and 8.17 ± 6.37, respectively, in malignant nodules. The area under the curves (AUCs) were calculated as 0.68, 0.61 and 0.67 for VI, FI and VFI, respectively. At optimal cut-off values of 10.2 for VI, 40.8 for FI and 5.5 for VFI, sensitivity and specificity were 72%/55.4%, 68%/57.1% and 68%/67.9%, respectively.

Conclusion: 3DPDUS could be useful in the characterization of thyroid nodules.
Key words: Thyroid nodules; three-dimensional power Doppler ultrasound; vascular indices; VOCAL

1. Introduction

Thyroid nodules are very common, and their prevalence increases with age. The prevalence of thyroid nodules ranges from 30-60% in autopsy series and 19-68% with high-resolution ultrasound (US) [1,2]. Despite the high prevalence of nodular thyroid disease, thyroid cancer is not a common condition. A risk for malignancy is observed in 7%–15% of cases, depending on factors such as age, sex, radiation exposure, family history and the levels of thyroid hormones [3–5]. Conventional US is the first-step imaging technique in the radiological evaluation of thyroid nodules. However, there is no single 100% reliable sonographic criterion for differentiating benign and malignant nodules at gray scale examination. A combination of gray scale characteristics is required in order to increase sensitivity and specificity, and fine needle aspiration (FNA) is needed for final diagnosis when suspected nodules are present. However, FNA is also subject to false positive or negative results, and material obtained at FNA may be non-diagnostic [6]. Additional and new imaging modalities are therefore needed for more accurate diagnosis. Color Doppler ultrasonography (CDUS), three-dimensional ultrasound (3DUS), three-dimensional power Doppler ultrasound (3DPDUS), contrast-enhanced ultrasound (CEUS) and sonoelastography are imaging techniques used in addition to conventional US.

Along with the developments in sonoelastography and 3D sonographic techniques, several different quantitative measurement parameters have been used in daily practice. The detection of elasticity index by elastography has been proposed as a supplementary tool in the assessment of thyroid nodules [7]. On the other hand, the use of 3DUS and 3DPDUS outside
Obstetric radiology has become increasingly widespread in recent years. Three-dimensional US, 3DPDUS and computer-aided color doppler software methods provide a number of advantages over conventional techniques [8,9]. Three-dimensional US is more accurate than two-dimensional examination in the evaluation of anatomical structures and assessment of disease and provides data that can be subjected to repeated evaluation [8,9]. Three-dimensional power Doppler US is able to quantify vascularity within organs, tissues and tumors [10,11]. From the data obtained with 3DPDUS, vascular indices can be calculated using VOCAL (Virtual Organ Computer-aided AnaLysis) software, and tissue vascularization can be shown with numerical values using these indices. This software provides three automatically calculated vascular indices; the vascularization index (VI), the flow index (FI) and the vascularization flow index (VFI) [12].

Numerous studies have investigated benign-malignant differentiation in gynecological and breast masses using 3DPDUS [11,13–16]. However, to the best of our knowledge, few studies have evaluated thyroid nodules using 3DUS and 3DPDUS [17–20]. Of these, only one has assessed thyroid nodule vascularization in a quantitative manner [18]. The purpose of this study was to investigate the diagnostic value of vascular indices obtained using 3DPDUS in differentiating benign and malignant thyroid nodules.

2. Materials and Methods

2.1. Subjects

The present study was approved by the local ethical committee and informed consent of the patients were obtained. One hundred and fourteen thyroid nodules with mixed (peripheral and central) vascularization patterns and the largest diameter of between 10 mm and 30 mm in 90 patients referred for FNA were prospectively assessed using 3DPDUS. This largest diameter criterion was intended to eliminate the volumetric discrepancy between benign and malign
nODULES. On the other hand, small nodules less than 10 mm could not be evaluated properly using power Doppler. Definite diagnosis (benign or malignant nodule) was made with FNA and/or histopathological analysis after surgery. Thirty-three nodules were excluded from the study due to retrosternal extension (n=13), non-diagnostic material (n=11), or respiratory or carotid pulsation artifacts (n=9). The final study group included 81 nodules in 67 patients (56 female, 11 male; aged 22-61 years; mean age, 44.6).

2.2. **Ultrasound examination**

Examinations were performed using a Voluson 730 Expert (General Electric, Waukesha, Wisconsin) device with a 6–12 MHz volumetric linear probe. In order to standardize our evaluation of nodule vascularization, same power Doppler settings were used. After visualization of the thyroid nodule in a 2D view, patients were requested to hold their breath for approximately 20 s, and 3D static power Doppler scanning was performed using the widest scanning angle (29º) covering the entire thyroid nodule (Figure 1). These acquired volume data were analyzed using VOCAL software. The outer margins of the nodule were drawn manually on a fixed axis with a 15º angle of rotation by the same radiologist (Figure 2). When all contours had been traced, the volume and three vascular indices (VI, FI and VFI) of the thyroid nodule were calculated automatically using the histogram facility in the VOCAL software (Figure 3). VI represents the ratio of color voxels to all voxels and shows the density of vessels. FI is the sum of weighted color voxels divided by the number of all color voxels and reflects mean color intensity. VFI represents the sum of weighted color voxels divided by all voxels and represents vascularization and perfusion [12].

2.3. **Statistical analysis**

The means and ranges of nodule size, volume and vascular indices of benign and malignant nodules were calculated. The vascular indices of the benign nodules were
compared with the vascular indices of the malignant nodules using the independent samples test. The optimum cutoff values for the differentiation of benign and malignant nodules were determined using receiver operating characteristic (ROC) analysis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC) for vascular indices were calculated with a 95% confidence interval. A p value <0.05 was considered statistically significant.

3. Results

Fifty-six (69%) of the nodules included in the study were diagnosed as benign and 25 (31%) as malignant. Analysis of the histopathology results revealed that all the malignant nodules were papillary carcinoma. Nineteen of the cases of benign nodule were nodular colloidal goiter, two were lymphocytic thyroiditis and two were Hurthle cell adenoma, the remaining cases being diagnosed as benign histopathology.

The mean age of the group with benign nodules was 46.4±7.7 years, compared to 40.7±13.2 in the group with malignant nodules. No statistically significant difference was determined between the two groups with regard to age (p= 0.53). The mean volume of benign nodules was 4.22 cm³, compared to a mean volume of 4.11 cm³ in malignant nodules in this study of nodules with the largest diameters of 1-3 cm. The difference in mean volumes between the two groups was not statistically significant (p= 0.94). When the groups were evaluated in terms of nodule content, 32 of the benign nodules were solid (58%), 24 of them were solid predominant (42%), while 18 of the malignant nodules were solid (72%), 6 of them were solid predominant (24%) and 1 of them were cystic predominant (4%). Vascular indices were significantly higher in malignant nodules compared to benign nodules (p<0.05). In the benign nodules, mean VI was 11.61 ± 6.88, mean FI 39.75 ± 3.93 and mean VFI 4.82 ± 2.94.
In the malignant nodules, mean VI was 18.64 ± 12.81, mean FI 41.82 ± 4.43 and mean VFI 8.17± 6.37 (Table 1).

Area under the ROC curve (AUC) values for VI, FI and VFI were 0.68, 0.61 and 0.67, respectively. ROC curves of the vascular indices are shown in Figures 4-6. At an optimal threshold value of 10.2 for VI, sensitivity was determined at 72% and specificity at 55.4%. At an optimal threshold value of 40.8 for FI, sensitivity was 68% and specificity 57.1%, while at an optimal threshold value of 5.5 for VFI, sensitivity was 68% and specificity 67.9%. The acquired diagnostic values for three vascular indices with using of stated cutoff values are given in Table 2.

4. Discussion

This study investigated the diagnostic value of 3DPDUS in differentiating between benign and malignant thyroid nodules. We analyzed the relations between nodule characterization and vascular indices (VI, FI and VFI) obtained using VOCAL software. A statistically significant difference was observed in terms of vascular indices between benign and malignant nodules, these indices being higher in malignant nodules.

Two-dimensional color or power Doppler US have been used in the characterization of thyroid nodules in numerous studies, and central vascularization that more commonly increases in malignant nodules can be examined subjectively using these methods [7,21–23]. With the increasing use of 3DPDS in clinical research, mass vascularization can now be evaluated quantitatively, and significant differences are determined in the differentiation of benign and malignant lesions [11,13–16]. To the best of our knowledge, apart from the present research, Li et al. performed quantitative evaluation of benign and malignant nodules by using VOCAL software [18]. In contrast to the findings of our study, they reported higher
vascular indices in benign nodules. However, considering the tumoral vascularity of thyroid and non-thyroid masses, we think that these results are inconsistent [13–16,24–26]. In a study using a computer-aided color doppler software, Baig et al developed a new method that divided thyroid nodule into central and peripheral regions and computed the regional and entire vascular index (VI) of the nodule [9]. They found that the mean VI of malignant nodules was significantly higher than that of benign nodules, in agreement with our study [9].

On the other hand, studies involving the characterization of thyroid nodules with CEUS in which the microvascular flow pattern is evaluated in tumoral lesions support our own findings [24–26]. In a study of 46 patients, Nemec et al. observed a significant difference in contrasting between benign and malignant nodules and determined sensitivity of 76.9%, specificity of 84.8% and accuracy of 82.6% for CEUS based on ROC analysis [26]. The reconstruction and segmentation of CEUS imaging data indicated that malignant nodules have a higher internal vasculature [24] and a higher vascular density than benign nodules. Since the vascular indices obtained using 3DPDUS show the percentage of vascularized tissue and mean blood flow rate in tissue, we hypothesize that it can also be used for assessing tumoral angiogenesis with detected CEUS without using contrast material. In this study, which included suspected nodules with a mixed vascularization pattern with CDUS, although the vascularization patterns was subjectively similar, the fact that vascular indices of malignant nodules were relatively higher than those of benign nodules supports our hypothesis. Based on ROC analysis, the sensitivity of vascular indices was approximately 68% - 72% and the specificity 55% - 68%.

Malignant thyroid nodules tend to have rich intralesional vascularization with anarchic structure [25]. The vascular network in thyroid nodules can be visualized with 3DPDUS, although when the entire lesion is included in the examination, peripheral and central vascularization can overlap, particularly in intensely vascularized nodules. In order to
eliminate this possibility, Slapa et al. identified risk factors for thyroid cancer using thin-slice volume rendering together with gray scale and 3DPDUS [17]. That study analyzed the relationship between the central vascular density of thyroid nodules and malignity, and reported that central vascular density was 75-81% sensitive and 49-56% specific in identifying thyroid cancer. A combination of contrast-enhanced US and 3DUS permits a more detailed evaluation of the vascular tree [24,26]. Molinari et al developed an image processing technique for skeletonization of intranodular vascularization using 3DCEUS [25]. The parameters involved in the skeletons were number of vascular trees, vascular density, number of branching nodes, mean vessel radius, tortuosity and the inflection count metric. According to that study, malignant nodules had a higher number of vascular trees and branches and higher vascular density [26]. These results indicate that malignant lesions are perfused by a dense vascular bed, and this is in agreement with our results. Those authors reported that quantification of nodule vascularization with skeletonization using 3DCEUS may be a useful technique in the differential diagnosis of thyroid lesions [25]. However, to the best of our knowledge, no study has used this thin-slice reconstruction technique in comparing the effectiveness of non-contrast 3DPDUS and 3DCEUS. We think that for a more conclusive statement further studies are needed to investigate this. Since the VOCAL software does not permit thin-slice rendering, vascular trees could not be evaluated in detail together with vascular indices.

The present study has some limitations. The first involves the known deficiencies of ultrasound, depending on the operator and patient. Artifacts deriving from respiratory movements and carotid pulsation prevented us obtaining appropriate images in some patients. The second limitation is that the histopathological results from all malignancies indicated papillary carcinomas and the number of malignant lesions was lower than that of benign lesions. The third limitation is the exclusion of the nodules smaller than 1 cm or larger than 3
cm in diameter in order to reduce the volumetric effect on vascularization. The final limitation is that this technique is not appropriate for nodules with retrosternal extension.

In conclusion, vascular indices obtained using 3DPDUS provide useful and quantitative analysis for the differentiation of benign and malignant thyroid nodules without contrast agent administration. Further studies are needed to determine the contribution of 3DPDUS to conventional US and to compare the efficacy of CEUS and 3DPDUS in the characterization of thyroid nodules.

References


Table 1. The comparison of nodule volume (NV) and vascular indices between benign and malignant thyroid nodules

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>NV( cm³)</td>
<td>4.2 ± 0.1</td>
<td>4.1 ± 0.9</td>
<td>0.94</td>
</tr>
<tr>
<td>VI</td>
<td>11.61 ± 6.88</td>
<td>18.64 ± 12.81</td>
<td>0.015</td>
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<tr>
<td>FI</td>
<td>39.75 ± 3.93</td>
<td>41.82 ± 4.43</td>
<td>0.039</td>
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<tr>
<td>VFI</td>
<td>4.82 ± 2.94</td>
<td>8.17 ± 6.37</td>
<td>0.018</td>
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</table>

Values are given as mean values ± SD; p: significance level for all pairs
Table 2. Results of Receiver Operating Characteristic (ROC) Analysis for vascular indices.

<table>
<thead>
<tr>
<th>Cutoff Level</th>
<th>Sensitivity(%)</th>
<th>Specificity(%)</th>
<th>PPV(%)</th>
<th>NPV(%)</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>10.2</td>
<td>72</td>
<td>55.4</td>
<td>41.9</td>
<td>81.6</td>
<td>0.68</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.415-0.687</td>
</tr>
<tr>
<td>FI</td>
<td>40.8</td>
<td>68</td>
<td>57.1</td>
<td>41.5</td>
<td>80</td>
<td>0.61</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td>0.432-0.703</td>
</tr>
<tr>
<td>VFI</td>
<td>5.5</td>
<td>68</td>
<td>67.9</td>
<td>48.6</td>
<td>82.6</td>
<td>0.67</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.540-0.797</td>
</tr>
</tbody>
</table>

AUC: Area Under Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value; CI: Confidence Interval
Figure Legends;

**Figure 1:** Sonogram showing 3D power Doppler acquisition in the axial plane using 3D power Doppler ultrasound. The power Doppler box was positioned so as to cover the entire thyroid nodule. The widest scanning angle (29º) including the whole thyroid nodule was used.

**Figure 2:** Using the manual contour method in the VOCAL technique, the outer margins of the nodule were drawn on a fixed axis with a 15º angle of rotation. Once all contours had been traced, the volume of the nodule was calculated automatically (the volume of the thyroid nodule can be seen in the lower right-hand corner).

**Figure 3:** Three-dimensional power Doppler images were analyzed using VOCAL histogram software. The results of the histogram analysis of the thyroid nodule show values for the vascularization index (VI), flow index (FI) and vascularization flow index (VFI).

**Figure 4:** Graph showing the receiver operating characteristic curve for VI.

**Figure 5:** Graph showing the receiver operating characteristic curve for FI.

**Figure 6:** Graph showing the receiver operating characteristic curve for VFI.
Figure 1

Figure 2
Figure 3

Figure 4
Figure 5

Figure 6