Optimized quantification of thyroid nodular vascularization from 3-D contrast-enhanced ultrasound images

C. Caresio1, M. Caballo1, M. Deandrea2, R. Garberoglio1, A. Mormile2, R. Rossetto4, P. Limone2, F. Molinari1

1Biolab, Department of Electronics and Telecommunication, Politecnico di Torino, Turin, Italy
2Endocrinology Section “Umberto I” Hospital, Ordine Mauriziano di Torino, University of Turin, Turin, Italy
3Fondazione Scientifica Mauriziana ONLUS, Torino, Italy
4Division of Endocrinology, Diabetology and Metabolism, Department of Medical Sciences, University of Turin, Turin, Italy

Introduction

Thyroid nodules represent a common finding in clinical practice and occur in up to 50% of the worldwide population. Even if the number of new thyroid cancers has considerably risen in the last decade, only 5% of thyroid nodules are malignant (incidence: 2.1%, mortality 0.5%, Globocan 2012). Differential diagnosis is, therefore, of paramount importance for a correct treatment of the nodule. Conventional ultrasound imaging has a moderate diagnostic accuracy (sensitivity: 68-100%, specificity: 67-94%, [1]) in the differentiation of thyroid nodules, and it must be coupled to fine needle aspiration (FNA) biopsy. However, FNA biopsy is an invasive procedure subject to inconclusive diagnosis in about 25% of the cases [2], possibly leading to overtreatment and unneeded surgery.

Contrast-enhanced ultrasound imaging (CEUS) has been introduced to improve the differential diagnosis of solitary thyroid nodules [1], [3], [4]. CEUS results in a better vasculature representation of thyroid healthy tissue and nodules compared with conventional Doppler imaging ([1], [5]). CEUS can boost the differential diagnosis of thyroid nodules if a quantitative and robust characterization of the vascularization is made possible.

Hence, the aim of our study was to develop a quantitative methodology for 3-D analysis of thyroid nodules’ vascular network based on 3-D CEUS images. In this work, we improved a previous method [5] by optimizing the representation of the vascular tree.

Methods

Patients and ultrasound equipment

Twenty patients (3 Males, age 43.00 ± 10.40 y, 17 Females, age 46.00 ± 13.28 y) with solitary solid thyroid nodule were selected in the study. All subjects underwent a clinical examination, hormonal profiling, and FNA biopsy. Among the 20 nodules, 10 were benign and 10 had confirmed histological diagnosis of malignancy. 3-D CEUS volumes were acquired after the injection of 2.5-ml ultrasound contrast agent (SonoVue Bracco, Milan, Italy) using a MyLab™ Twice ultrasound device (Esaote, Genova, Italy), equipped with a linear-volumetric array transducer with 4-13 MHz variable frequency.

3-D vascular segmentation algorithm

We developed an innovative technique for rapid and automated representation and quantification of cancer vascular architecture. The algorithm consists of the following steps: i) starting from the CEUS volume (Figure 1.b) an initial step of preprocessing based on a Vessel Enhancement Filter [6] for noise suppression and contrast improvement (Figure 1.c) is performed; ii) a 3-D iterative thinning process is used to obtain the
morphological skeleton of the tumor vascular network (Figure 1.d); iii) a mathematical-based centerline extraction is applied [7] (Figure 1.e and 1.f). The skeleton in Figure 1.f is used for the quantitative analysis.

Figure 2: Vascular segmentation algorithm steps: (a) B-Mode slice of a malignant nodule; (b) CEUS slice; (c) Vessel enhancement filtering; (d) Morphological skeleton (e) Intensity flow centerline (f) 3-D skeleton rendering.

**Features extraction and data analysis**

Seven features were calculated from the 3-D skeleton. The first three were tortuosity metrics [8]: Distance Metric (DM), Inflection Count Metric (ICM) and Sum Of Angles Metric (SOAM). The last four were architectural parameters [9]: number of trees (NT), number of branches (NB), vascular volume density (VVD) and spatial vascularity pattern (SPV). The parameter SPV provided a discrete result of the spatial distribution of blood vessels in the tumor as perilesional or intranodular. For the two group of tumors, mean values and standard deviation for the continuous features were reported. The comparison between benign and malignant nodules was performed using a non-parametric Mann-Whitney U-test.

Multivariate Analysis of Variance (MANOVA) was used to test the equality of the means between benign and malignant nodules, considering the patient age, patient gender and the seven vascular features.

**Results**

In Table 1, mean values ± standard deviations of the six continuous features and the discrete parameter SVP are reported for the two nodules groups. Vascular continuous parameters are all higher for malignant nodules. The result of the Mann-Whitney U-test shows a significant difference between the benign and malignant nodules. For the SVP feature, 6 out of 10 benign nodules were labelled as perilesional while malignant nodules were all classified as intranodular (10/10). To conduct MANOVA, after removing the collinear variables, five features were left (ICM, VVD, NT, SVP and patient age). The MANOVA dimension of the group means was equal to 1 (p << 0.001), which indicated that, in the MANOVA hyperplane, the first canonical variable is discriminant for the nodule type and benign and malignant nodules can be linearly separated (Figure 2).
Table 1: Mean values ± standard deviation and p-value of the 6 vascular features analyzed for CEUS volumes. The SVP is reported as a fraction of perilesional benign tumor and intranodular malignant tumors on the total number of tumor of the respective group.

<table>
<thead>
<tr>
<th>CEUS</th>
<th>Benign Nodules</th>
<th>Malignant Nodules</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (a.u.)</td>
<td>13.91 ± 8.31</td>
<td>82.93 ± 49.38</td>
<td>&lt;&lt; 0.05</td>
</tr>
<tr>
<td>ICM (a.u.)</td>
<td>35.78 ± 18.63</td>
<td>227.62 ± 93.97</td>
<td>&lt;&lt; 0.05</td>
</tr>
<tr>
<td>SOAM (a.u)</td>
<td>4.28 ± 3.19</td>
<td>26.51 ± 21.19</td>
<td>&lt;&lt; 0.05</td>
</tr>
<tr>
<td>VVD (%)</td>
<td>30.30 ± 11.40</td>
<td>60.30 ± 7.11</td>
<td>&lt;&lt; 0.05</td>
</tr>
<tr>
<td>NT (a.u.)</td>
<td>5.30 ± 1.34</td>
<td>8.40 ± 2.79</td>
<td>&lt;&lt; 0.05</td>
</tr>
<tr>
<td>NB (a.u.)</td>
<td>18.30 ± 5.83</td>
<td>53.70 ± 17.72</td>
<td>&lt;&lt; 0.05</td>
</tr>
<tr>
<td>SVP (a.u.)</td>
<td>6/10</td>
<td>10/10</td>
<td>&lt;&lt; 0.05</td>
</tr>
</tbody>
</table>

Conclusions

In this work, a new methodology applied on 3-D contrast-enhanced ultrasound images was presented in the characterization of thyroid nodules. Innovative image processing techniques combined with vascular features extraction enabled the assessment of thyroid nodules; in fact, malignant lesions showed higher vascular features compared to benign nodules. These findings suggest that malignant lesions are highly perfused due to the increase in the overall density of the vasculature in the lesion. In future work, the proposed methodology could be extended and applied to CEUS volumes in the characterization and localization of prostate cancer, complementing existing dynamic CEUS features [10], [11].
References