Roles of gray-scale, Color-Doppler ultrasound and sonoelastography for assessment of thyroid nodules: nodule size correlation

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Abstract
Objective: To evaluate the predictive value of roles of gray-scale, color-Doppler ultrasound, and sonoelastography for the assessment of thyroid nodule to determine whether nodule size affects the differential diagnosis of benign and malignant, with fine needle aspiration cytology analysis as the reference standard.
Methods: A total of 270 consecutive patients (mean age, 35±55 years; range, 30-50 years; 25males and 245 females) with 300 thyroid nodules were examined by gray-scale, color-Doppler ultrasound, and 100 patients examined by sonoelastography in this prospective study. All patients underwent surgery and the final diagnosis was obtained from fine needle aspiration cytology analysis.
Results: Three hundred nodules (206 benign, 94 malignant) were divided into small (SNs, ≤1cm, n=124) and large (LNs, >1Cm, n=178) nodules. Microcalcifications were more frequent in malignant LNs than in malignant SNs, but showed no significant difference between benign LNs and SNs. Poorly-circumscribed margins were not significantly different between malignant SNs and LNs, but were less frequent in benign LNs than in benign SNs. Among all nodules, marked intranodular vascularity was more frequent in LNs than in SNs. By comparison, shape ratio of anteroposterior to transverse dimensions (A/T) ≥1 was less frequent in LNs than in SNs. Otherwise, among all nodules, marked hypoechoogenicity and elasticity score of 4-5 showed no significant difference between LNs and SNs.
Conclusions: The predictive values of microcalcifications, nodular margins, A/T ratio, and marked intranodular vascularity depend on nodule size, but the predictive values of echogenicity and elastography do not depend on nodule size.
Key words: Elastography; Thyroid nodules; Ultrasound. Malignant. Nodule size.

I. Introduction
Thyroid nodules are one of the mostly encountered medical problems that need precise diagnosis and specification prior to decision making regarding treatment. They are found in 4%-8% of adults by palpation, 41% by ultrasonography (US), and 50% by pathologic postmortem examination. The prevalence of thyroid cancer is as high as 5%-10%. [1], and in other literature it is about 5% 1-3 [2] Papillary carcinoma is the most common (75%-80%). Other types include follicular carcinoma (10%-20%), medullar carcinoma (3%-5%), and an plastic carcinoma (1%-2%). Lymphoma and metasteses of the thyroid gland are not common. [1]

Ultrasoundography has been used for decades to diagnose thyroid nodules and to select cases for fine needle aspiration biopsy (FNAB) in which malignancy is suspected. However, conventional US are not as useful for differentiating benign and malignant nodules. [3, 4, 5] In addition, the sensitivity, specificity, negative and positive predictive values are considerably variable from study to another. [6, 7, 8] FNAB provides the best method to differentiate benign from malignant nodules. [9] although it is recommended for all nodules with a diameter more than 1 cm, and in smaller nodules having findings suggestive of malignancy. It is estimated that about 250,000 : 300,000 thyroid FNA biopsies are performed in the United States every year. However, a large percentage (approximately 70%) of these biopsies turns out to be benign. [10] In some literatures, 15% to 30% of samples obtained by FNAB are classified as indeterminate, and patients are referred for thyroïdectomy or lobectomy. Thyroid carcinoma is ultimately confirmed in less than 20% of these cases leaving unsatisfactory diagnostic workup of thyroid nodules. [11] In addition, US-guided FNAB is an invasive procedure that has disadvantages e.g. sampling errors, time and money consumption, painful, not easy to be performed for very small nodules and it is associated with minor complications. [12] Palpation is a basic and important method in the assessment of thyroid nodules. Malignant nodules tend to be much harder than benign ones. However, the stiffness of thyroid nodules in palpation is subjective and can't be an accurate indicator for malignancy [13] although there are many criteria that are indicator for malignancy using conventional Ultrasound e.g. nodule echogenicity, microcalcification, blurred or speculated margin, absent halo sign and abnormal vascularity, yet it
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does not provide direct information about the hardness of a nodule. Ultrasound elastography (USE) was
developed to obtain information on tissue stiffness noninvasively. It was first applied for characterization
of breast lesions, and recently it is applied for prostatic and thyroid tumors. USE is based on the reconstruction
of tissue stiffness by measuring the degree of tissue’s deformation in response to the application of an external
force. The softer parts of tissues deform easier than the harder parts under compression, thus allowing an
objective determination of tissue stiffness. This technique has been shown to be useful in the differential
diagnosis between benign and malignant tumors. Most malignant tumors are stiff and hard compared to the
surrounding normal tissues, while most benign tumors are softer. Many scoring systems were applied to
reflect tissue elasticity; the most feasible of them is that of Itoh A et al, 2006 who assigned 5 scores depending
of the color shown by the tissue when it is subjected to pressure. Tissue stiffness on USE was scored from
1 (greatest elastic strain) to 5 (no strain) based on subjective analysis of the elastogram images and color. This
scoring system was used to differentiate benign and malignant lesions as shown in table 1. The purpose of this study was to define the roles of gray-scale, color-Doppler ultrasound, and sonoelastography
for assessment of thyroid nodules to determine if nodule size affects differential diagnosis of benign and
malignant using FNAC as the reference standard.

II. Patients and methods:

“Patients”, This is prospective study after obtaining an ethical approval, 300 patients were included in this
study (30 males and 270 females) ranging in age from 19 to 75 years; with the mean age are 43. The study was
done at the diagnostic radiology department, KAUGH during the 2011-2013 year. All patients provided written
consent before they were subjected to grey scale US and Doppler study followed by free hand USE using a
real-time scale of 1 to 5, where 5 corresponds to the highest tissue stiffness. Tissue stiffness on USE was scored
into five scores according to Ueno E, 2006. All cases were done using i22 Philips US machine and high
frequency (5-12 MHz) linear probe. Images were taken before and after compression. The color scale varied
from red (softest tissue) to blue (hardest tissue). Although many patients had multiple nodules, yet we applied
USE for the most suspicious ones only. 30 patients were excluded from the study either because they refused
FNAB or due to insufficient sample from tiny nodules. So, the remaining 270 were only included in the study
(145 females and 25 males). FNA biopsy/ cytology were done by an expert radiologist under strict aseptic
conditions, using local anesthesia and appropriate needles. Written consent was provided by every patient. All
specimens were referred to the central laboratory department at KAUGH for interpretation.

“Statistical analysis”, Demographic patients data together with USE results and FNAB results were collected
and Statistical analyses were performed using the IBM SPSS Statistics version 21.0 (IBM Company, New York,
USA) software package. Frequency tables were analyzed using the Chi-square test (X2). To assess the
diagnostic value (sensitivity and specificity) of ultrasound elastography compared with the cytological results,
cross-tabulation tests were performed.

“Conventional ultrasound and sonoelastography”, both conventional sonography and sonoelastography were
performed using i22 Philips US machine and high frequency (5-12 MHz) linear probe. All examinations were
performed by the same investigator with ten years of experience in thyroid ultrasound. All selected thyroid
nodules were assessed by conventional gray-scale and color-Doppler ultrasound. The echogenicity of the
nodules was classified into four categories: marked hypoechogenicity, hypoechochogenicity, isoechochogenicity,
and hyperechochogenicity. The marked hypoechochogenicity was defined as low echogenicity compared with the
surrounding strap muscles. The hypoechochogenicity, isoechochogenicity, and hyperechochogenicity were defined
according to the comparative echogenicity between the thyroid parenchyma and the nodule. Shape was assessed
as the ratio of anteroposterior (A) to transverse (T) dimensions (A/T≥1 or <1). The margin of the nodule was
described as (1) well-circumscribed when the boundary of the nodule was well-defined or the contour of the
nodule was smooth and rounded; or (2) poorly-circumscribed when the boundary of the nodule was ill-defined
or the contour of the nodule was irregular with jagged edges. Calcification within the nodule was classified into
categories: no calcification, microcalcification, large and dense calcification, and rim calcification. Microcalcification was defined as hyperechoic spots less than 2 mm with or without acoustic shadowing. The component of the nodule was classified as solid (solid portion>90%), predominantly solid (solid portion>50%), predominantly cystic (cystic portion>50%), and cystic (cystic portion>90%). The presence and the pattern of blood flow evaluated by color-Doppler imaging were classified as follows: no vascularity-defined as no color-Doppler flow in the periphery or within the nodule; peripheral vascularity-defined as flow in the peripheral position and absent or slight flow in the central part of the nodule; marked intranodular vascularity-defined as more flow in the central part of the nodule than at the periphery. (24).
“Sonoelastography”, was performed after the conventional sonographic examination by the same investigator. With the use of sonoelastographic mode, the probe was placed on the neck with light pressure, and an elastographic region of interest (ROI) was positioned by the operator that included the nodule and sufficient surrounding thyroid tissue to be evaluated. To keep the strain distribution uniform, the probe was pressed to the area with a frequency of 2 to 3 times per second during the cycle of compressing-decompressing in elastography. The level of the pressure was indicated by a 5-point scale meter, which was displayed in real time on the screen. A scale of 2 to 4 was indicative of correct compression. The real-time elastogram was displayed over the gray-scale imaging in a color-coded map: highly elastic tissues (soft) appear in red, less elastic tissues (hard) appear in blue, and intermediate degrees of elastic tissues are shown in green. The sonoelastogram was considered to be reliable only when the elastographic image displayed over the B-mode continued for at least 5 s with the illuminated indicator showing a value between 2 and 4. In our study, the characteristics of thyroid nodules on sonoelastogram were categorized into 5 patterns (i.e., elasticity scores 1–5). Fig. (1).

Fig (1) shows elasticity scoring RTE (USE) (25-26).

III. “Results”,

Two-hundred and seventy patients with 300 thyroid nodules were successfully evaluated by gray-scale, color-Doppler ultrasound, and 100 patients by sonoelastography. All thyroid nodules were confirmed FNAC by means of surgery. There were 191 benign (71%) and 79 malignant (29%) nodules. In the 81 patients having multiple thyroid lesions, 28 patients had multiple malignant nodules, 60 had multiple benign nodules, and 22 had both multiple benign and malignant nodules. The diagnoses of malignancy included papillary carcinoma (n=61), follicular carcinoma (n=10), anaplastic carcinoma (n=2), and medullary carcinoma (n=6). The diagnoses of benign nodules included nodular goiter (n=174), thyroiditis (n=8), sub acute thyroiditis (n=4), follicular adenoma (n=3), and atypical adenoma (n=2). The mean maximal diameter of the malignant nodules (1.4±0.9 cm, range from 0.5 to 5cm) was significantly smaller than that of the benign nodules (1.7±1.2 cm, range from .5 to 5.4 cm) (P=0.002).

“Ultrasound features of nodules vs. nodule size”, To evaluate the relationship between nodule size and ultrasound features, a cutoff of 1cm was set as a criterion for dividing small and large nodules. Based on the pathologic findings, there were 111 small nodules (SNs) (malignant 50, benign 61) and 159 large nodules (LNs) (malignant 59, benign 100). The findings of ultrasound features in malignant and benign nodules within SN and LN groups are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>M (50)</th>
<th>B (61)</th>
<th>M (59)</th>
<th>B (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly-circumscribed margin</td>
<td>21(42%)</td>
<td>16(32%)</td>
<td>5(8%)</td>
<td>24(24%)</td>
</tr>
<tr>
<td>Marked hypoechogenicity</td>
<td>56(34%)</td>
<td>17(29)</td>
<td>5(8%)</td>
<td>8(8%)</td>
</tr>
<tr>
<td>Microcalcification</td>
<td>23(46%)</td>
<td>16(32%)</td>
<td>41(69%)</td>
<td>10(10%)</td>
</tr>
<tr>
<td>A/T≥1</td>
<td>27(54%)</td>
<td>18(30%)</td>
<td>5(8%)</td>
<td>3(3%)</td>
</tr>
<tr>
<td>Marked intranodular</td>
<td>25(50%)</td>
<td>4(7%)</td>
<td>25(42%)</td>
<td>30(30%)</td>
</tr>
</tbody>
</table>
Roles of gray-scale, Color-Doppler ultrasound and sonoelastography for assessment of thyroid vascularity.

<table>
<thead>
<tr>
<th>Elasticity score of 4–6</th>
<th>10(20%)</th>
<th>3(5%)</th>
<th>50(85%)</th>
<th>23(23%)</th>
</tr>
</thead>
</table>

n: number, M: malignant; B: benign; d: diameter.

“Diagnostic accuracy of ultrasound features for malignant nodules”, The diagnostic accuracy of the ultrasound features was evaluated separately for SNs and LNs (Table 2) for both SNs and LNs, the presence of marked hypoechogeticity, micro calcification, A/T≥1 ratio, and marked intranodular vascularity had a specificity of 77%–97% and a sensitivity of 8.5%–86%. In contrast, the elasticity score of 4–5 and poorly-circumscribed margin had a specificity of 71%–80% and a sensitivity of 89%–93%.

Table (2). Diagnostic accuracy of ultrasound findings for malignant nodules according to nodular size.

<table>
<thead>
<tr>
<th>d≥10mm:n=111 ns</th>
<th>Malignant (n = 50)</th>
<th>Benign, (n = 61)</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly-circumscribed margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoechogeticity</td>
<td>40</td>
<td>5</td>
<td>80</td>
<td>91</td>
<td>89</td>
<td>8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>23</td>
<td>16</td>
<td>46</td>
<td>73</td>
<td>58</td>
<td>26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intranodular blood flow</td>
<td>25</td>
<td>4</td>
<td>50</td>
<td>93</td>
<td>85</td>
<td>6.6</td>
<td>0.011</td>
</tr>
<tr>
<td>A/T ≥1 cm</td>
<td>27</td>
<td>18</td>
<td>54</td>
<td>70</td>
<td>60</td>
<td>29.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Elasticity score of 4-5</td>
<td>10</td>
<td>4</td>
<td>20</td>
<td>93</td>
<td>71</td>
<td>28</td>
<td>0.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>d&lt;10mm:n=159 ns</th>
<th>Malignant (n = 50)</th>
<th>Benign, (n = 61)</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly-circumscribed margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoechogeticity</td>
<td>51</td>
<td>24</td>
<td>86</td>
<td>76</td>
<td>68</td>
<td>32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>17</td>
<td>8</td>
<td>29</td>
<td>92</td>
<td>68</td>
<td>32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intranodular blood flow</td>
<td>41</td>
<td>10</td>
<td>69</td>
<td>90</td>
<td>80</td>
<td>20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>A/T ≥1</td>
<td>5</td>
<td>3</td>
<td>8.5</td>
<td>97</td>
<td>62</td>
<td>37.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Elasticity score of 4-5</td>
<td>50</td>
<td>23</td>
<td>84</td>
<td>77</td>
<td>68.5</td>
<td>31.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. (2) Real time ultrasound for 44 yrs old female with papillary carcinoma confirmed by FNA cytology.

Fig. (3) Real time ultrasound for 48 yrs old male with medullary carcinoma confirmed by FNA cytology.
IV. Discussion

The aims of our prospective study were to evaluate the predictive value of roles of gray-scale, color-Doppler ultrasound, and sonoelastography for the assessment of thyroid nodule to determine whether nodule size affects the differential diagnosis of benign and malignant. There is a general agreement that ultrasound features indicating a high risk for malignancy should be an indication for an FNAB. Ultrasound features predictive of malignant nodules include the presence of irregular margins, marked hypoechoicity, microcalcifications, taller-than-wide shape, intranodular vascularity (17, 20, 21, 22, 23, 24). Ultrasound evaluation of the border of a thyroid nodule can be classified as well-defined or ill-defined. An ill-defined and irregular or microlobulated margin is suggestive of malignancy, but the sensitivity (48.3%–84.4%) and specificity (81%–97.6%) are variable. Some investigators have suggested an ill-defined margin as the criterion for the discrimination of malignant from benign nodules, others have suggested an irregular or microlobulated margin as the criterion (20, 17, 23, 21, 23). Poor interobserver agreement when assessing margins may account for these discordant findings. An irregular and microlobulated contour is thought to be the hallmark of thyroid papillary cancers as the neoplastic thyroid follicular epithelia undergo disorganized growth, resulting in an irregular or lobulated appearance. An ill-defined margin may be associated with minimal marginal tumor infiltration of malignancy. Both characteristics suggest malignant infiltration of adjacent thyroid parenchyma with no pseudocapsule formation (17, 19, and 20). In our study, a poorly-circumscribed, ill-defined or irregular and microlobulated margin (Figs. 5 and 6), was found in 80% of malignant nodules and 34% of benign nodules. The sensitivity increased to 90% in SNs and 86% in LNs, the specificity was 66% in SNs and 76% in LNs, and accuracy exceeded 80%. The frequency of this characteristic had no significant difference between malignant LNs and SNs, but it was less frequent in benign LNs than in benign SNs. The hypoechoicogenicity of thyroid nodules is not a reliable sign of malignancy since the specificity and PPV are low (17, 18, and 21). Some studies have observed that marked hypoechoicogenicity was highly specific for diagnosing malignant nodules, but with low sensitivity. In this study, our findings are in accordance with previous studies. In addition, we also find that the predictive ability of marked hypoechoicogenicity was not relevant to nodular size. Microcalcification is one of the most specific features of thyroid malignancy with a specificity of 71.0%–98.8% (19, 20, 21, and 23). In this study, microcalcifications were more commonly observed in malignant LNs than in malignant SNs. This result was similar to that study (19, 22). In our study no significant difference was observed between benign LNs and SNs. Microcalcifications had a specificity of 73% and a sensitivity of 46% in SNs. In the LN group, the specificity increased to 90%, and the sensitivity increased to 69%. Therefore, microcalcifications may be more predictive of malignancy in LNs than in SNs. The ratio of the nodular shape A/T≥1 is a reportedly characteristic and very specific feature of malignant thyroid nodules (17, 20, 21, and 23). This appearance may be due to the fact that malignant nodules grow across normal tissue planes, while benign nodules grow parallel to normal tissue planes (20). In our study, we found that this feature was more sensitive in SNs than in LNs. Nearly 54% of malignant nodules. There are many reports that have evaluated the diagnostic performance of Doppler ultrasound in the assessment of thyroid tumors. Some authors claimed that intranodular vascularity is useful for differentiating benign from malignant thyroid nodules (19) while others disagreed (23). In our study, we defined marked intranodular vascularity as more flow in the central part of the nodule than at the periphery which resulted in a high specificity but a very low sensitivity. We found that the diagnostic accuracy was dependent on tumor size, in which marked intranodular vascularity was more commonly observed in LNs than in SNs in both malignant and benign nodules. Recent studies demonstrated that ultrasound-based elastography could improve detection of malignant thyroid nodules with a high sensitivity and good specificity (20, 19, and 23). In our study, the sensitivity of sonoelastography was 84% and specificity 1s 77% in LNs, which could be useful in determining which nodules could be safely observed without biopsy.
V. Conclusion:
The predictive values of microcalcifications, nodular margins, A/T ratio, and marked intranodular vascularity depend on nodule size, but the predictive values of echogenicity and elastography do not depend on nodule size.

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