Thyroid nodules echogenicity evaluation: a new paradigm?

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Authors: A. S. C. C. Germano¹, W. Schmitt², E. Rosado², R. M. R. Mateus-Marques²; ¹Oeiras/PT, ²Lisbon/PT
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Aims and objectives

The subjective assessment of echogenicity in thyroid nodules is currently performed in comparison to the echogenicity of normal thyroid parenchyma and anterior neck muscles (strap muscles and ECM) (1-4). A hypoechogenic nodule is more hypoechogenic than the normal thyroid parenchyma and is considered a suspicious risk factor by several guidelines (1,2).

But the majority of thyroid nodules are hypoechogenic and most of them are benign. (3)

In 2002 Kim (3) defined the concept of a marked hypoechogenic nodule as being more hypoechogenic than the thyroid parenchyma and than the adjacent strap muscles and also more suspicious of being malignant.

According to TIRADS score of Gilles Russ (5), when no other suspicious signs are present, a nodule that is less echogenic than the thyroid parenchyma, but more echogenic than the muscle has a malignancy risk of around 6%. If it is more hypoechogenic than the muscle, the risk will be 69%.

Even though anterior neck muscles are uniformly present in all patients, using them as a comparative standard would imply that they would be identical in every individual. We know that muscle echogenicity varies, namely according to the physical condition of the individual, gender and age. (6)

We pondered the possibility of there being a base difference in the neck muscles/thyroid/thyroid nodule echogenicity between distinct age groups or genders.

The aim of this work was to identify a possible significant difference between anterior neck muscles echogenicity and the in the relation between thyroid nodules and muscles echogenicity in different age groups or in different genders.
Methods and materials

In the period comprising July 10th 2013 and August 20th 2014, ultrasound-guided fine needle aspiration cytology (FNAC) was performed on 209 thyroid nodules to 194 consecutive patients at Hospital Professor Doutor Fernando Fonseca, E.P.E. (HFF).

In this prospective observational study we analysed the ultrasound images obtained from these patients.

The same radiologist performed all the examinations and the image analysis.

The scanner used was a GE Logic E9 (Milwaukee, Wisconsin, USA) with a ML linear probe with a range of 6 to 15 MHz.

The following parameters were present in the used pre-set: frequency - 11 MHz; dynamic range - 66; cross x beam - low; cross x beam type - near; SRI - HD2; grey map - F; suppression - 2; line density - 2; focus width - 2.

We attempted quantification of echogenicity by two different methods:

Method 1:

The measuring of intensity or echo level (EL) in decibels was made in all patients with the integrated ultrasound equipment built-in software, an easy-to-use utility.

EL displays the mean intensity (in decibels) of the pixels within the region of interest (ROI).

The dB is the unit used to describe the relative amplitude of echoes in ultrasound systems and is used to express ratios of intensity. (7).

Zero dB is the maximum intensity (hyperechogenic) and values become more and more negative as the structure becomes more hypoechogenic (8).

Several regions of interest were drawn: in the anterior neck muscles; in the normal adjacent thyroid parenchyma; and also in the more hypoechogenic solid component of the thyroid nodule. The ROI diameters varied according to the targeted structure.

Method 2:
In a sub-sample of 100 nodules, we recorded DICOM formatted images from the PACS (the same images used to measure EL). Those images was transferred to the osirix® program. A ROI was similarly drawn in the structures previously described, and we measured the mean grey scale level within it.

With the obtained data, we built a data set, "tiroide2014.sav" (n=209).

Patients were stratified in two groups according to age (#60 years and >60 years) and gender (male and female).

The statistical analysis was performed on IBM SPSS statistics, for Macintosh version 21. Non parametric Mann-Whitney test was used.

Significance was considered for p<0.05.
Results

1. Exploratory analysis of the variables

The obtained data set, dubbed "tiroide 2014", containing 14 variables related to 209 nodules, displays missing elements for the ec_thyroid; ec_nodule and ec_muscle variables, (n=100); for d_nodule, d_muscle and d_thyroid (n=205). The elements with missing values were excluded from the statistical analysis.

i. "cod_age" - variable "age" recoded with two categories: 0 - #60 years and 1 - >60 years.

ii. "gender" - patient gender: 0 = male; 1 = female.

iii. "d_nodule" - mean intensity (echo level) of the nodule's solid component, in dB.

iv. "d_thyroid" - mean intensity (echo level) of the thyroid, in dB. v. "d_muscle" - mean intensity (echo level) of the anterior neck muscle, in dB.

vi. "ec_nodule" - mean grey scale value of the ROI drawn on the nodule's solid component, in grey scale units.

vii. "ec_thyroid" - mean grey scale value of the ROI drawn on the normal thyroid parenchyma in grey scale units.

viii. "ec_muscle" - mean grey scale value of the ROI drawn on the anterior neck muscle in grey scale units.

ix. "Dbthy_nod" - variable calculated by subtracting the nodule's intensity from the thyroid's intensity.

x. "Dbthy_musc" - variable calculated by subtracting the muscle's intensity from the thyroid's intensity.

xi. "Dbnod_musc" - variable calculated by subtracting the muscle's intensity from the nodule's intensity.

xii. "Ecthy_nod" - variable calculated by subtracting the nodule's grey scale from the thyroid's grey scale.

xiii. "Ecthy_musc" - variable calculated by subtracting the muscle's grey scale from the thyroid's grey scale.
"Ecnod_musc" - variable calculated by subtracting the muscle's grey scale from the nodule's grey scale.

Of the 209 nodules, 41 (19.6%) belonged to male individuals and 168 (80.4%) to female individuals.

Nodule size ranged between 7 and 100 mm, the median being 20 mm.

Patient age varied from 7 to 90 years, for a median of 62.

100 nodules belonged to patients 60 years or less old (47.8%) and 109 nodules were present in patients older than 60 years (52.2%).

The nodules' intensity levels fell between -62 and -20.9 decibels, with a median of -39.8 dB. Concerning the thyroid parenchyma, intensity levels were positioned between -51.8 and -23.3 and the median was -37.2. Muscle intensity took values encompassing -56.5 and -23.3, for a median of -43 dB. Regarding the variables calculated from these values, it is of further notice that the intensity difference between the thyroid and muscle ranged from -13 to 23 (median 6.4); between the nodule and muscle it varied between -19 and 23 (median 3) and, for the thyroid and nodule, between -14 and 19 (median 4).

Looking at the sample wherein the grey scale was measured, thyroid values ranged from 5.9 to 154.96 grey scale units (median 78.06); the nodule's values varied between 29.95 and 167.38 (median 93.36) and the muscle's between 6.15 and 110.0 (median 60.26). Concerning the variation between the thyroid and muscle, it took values from -62 to 85 (median 19.33); -31 to 110 between the thyroid and nodule (median 37.3) and -70 to 100 between the nodule and muscle (median 14.54).
Fig. 1: patient gender distribution

References: Department of Radiology, HFF
Fig. 2: patient age groups distribution

References: Department of Radiology, HFF
Fig. 3: box plots of mean intensity (EL) distribution - all nodules

References: Department of Radiology, HFF
Fig. 4: box plots of mean grey scale distribution - all nodules

References: Department of Radiology, HFF

2. Assessment of the possible existence of a relationship between gender and muscle echogenicity/grey-scale

Taking into account the existence of asymmetric distributions and the presence of multiple outliers, we chose to use the median as our location measure and the minimum-maximum amplitude as dispersion measure for the quantitative variables. We also decided to use non-parametric Mann-Whitney test in our statistical evaluation.

In the next tables, we summarize the ultrasound images characteristics of the following variables: muscle, thyroid and nodule intensity; difference between the intensity of the
nodule and muscle; difference between the intensity of the nodule and thyroid; difference between the intensity of the muscle and thyroid. Muscle, thyroid and nodule grey scale and difference between the grey scale of the muscle and thyroid as well as thyroid and nodule and nodule and muscle, stratified in male and female genders.

<table>
<thead>
<tr>
<th></th>
<th>All (n=205)</th>
<th>Male (n=39)</th>
<th>Female (n=166)</th>
<th>P value $^\S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>D_thyroid</td>
<td>-37,20(-51,8;-23,3)</td>
<td>-38,10(-51,8;-23,3)</td>
<td>-37,05(-51,8;-23,3)</td>
<td>0,669</td>
</tr>
<tr>
<td>D_nodule</td>
<td>-39,90(-62,0;-20,9)</td>
<td>-38,2(-53,6;-28,1)</td>
<td>-40,4(-62,0;-20,9)</td>
<td>0,205</td>
</tr>
<tr>
<td>D_muscle</td>
<td>-43,10(-66,5;-23,3)</td>
<td>-43,10(-51,1;-31,6)</td>
<td>-42,95(-62,0;-23,3)</td>
<td>0,955</td>
</tr>
<tr>
<td>Db_thy-nod</td>
<td>4,00(-14;19)</td>
<td>2,20(-9;13)</td>
<td>4,30(-14;19)</td>
<td>0,237</td>
</tr>
<tr>
<td>Db_thy-mus</td>
<td>6,4(-13;23)</td>
<td>5,60(-7;18)</td>
<td>6,45(-13;23)</td>
<td>0,800</td>
</tr>
<tr>
<td>Db_nod-mus</td>
<td>3(-19;23)</td>
<td>5,20(-17;16)</td>
<td>2,80(-19;23)</td>
<td>0,233</td>
</tr>
</tbody>
</table>

**Table 1** Intensity mean values, stratified by patient gender (median; min-max).

$^\S$Mann Whitney

<table>
<thead>
<tr>
<th></th>
<th>All (n=100)</th>
<th>Male (n=25)</th>
<th>Female (n=75)</th>
<th>P value $^\S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ec thyroid</td>
<td>93,36(29,45;167,23)</td>
<td>88,12(43,44;167,23)</td>
<td>93,46(29,94;160,13)</td>
<td>0,694</td>
</tr>
<tr>
<td>Ec nodule</td>
<td>78,05(5,89;154,96)</td>
<td>78,67(32,75;139,45)</td>
<td>76,88(5,89;154,96)</td>
<td>0,777</td>
</tr>
<tr>
<td>Ec muscle</td>
<td>60,26(6,15;109,90)</td>
<td>54,13(12,04;98,82)</td>
<td>61,36(6,15;109,90)</td>
<td>0,314</td>
</tr>
<tr>
<td>Ec thy-nod</td>
<td>19,33(-62;85)</td>
<td>10,02(-41;81)</td>
<td>19,87(-62;85)</td>
<td>0,350</td>
</tr>
<tr>
<td>Ec thy-musc</td>
<td>37,30(-31;110)</td>
<td>40,83(-11;91)</td>
<td>36,89(-31;110)</td>
<td>0,659</td>
</tr>
<tr>
<td>Ec nod-mus</td>
<td>14,54(-70;100)</td>
<td>17,56(-44;100)</td>
<td>13,94(-70;81)</td>
<td>0,452</td>
</tr>
</tbody>
</table>

**Table 2** Grey scale mean values, stratified by patient gender (median; min-max).

$^\S$Mann Whitney
We noted that the distribution within the patient gender category contained no statistical significance for any of the variables in either of the measurement methods performed.

3. Assessment of the possible existence of a relationship between age and muscle echogenicity/grey-scale

An identical analysis was performed, stratifying the patients in two age groups: ≤ 60 years and > 60 years, for these variables: muscle intensity; thyroid intensity; nodule intensity; difference between the intensity of the nodule and muscle; difference between the intensity of the thyroid and muscle; difference between the intensity of the thyroid and nodule; muscle, nodule and thyroid grey scale, and difference between the grey scale of the thyroid and muscle, thyroid and nodule as well as nodule and muscle.

The obtained results are summarized in the following tables.

![Table 3](image_url)

$^\S$ Mann Whitney.
Table 4 Grey-scale mean values, stratified by age groups (median; min-max).

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ec thy-musc</td>
<td>37.30</td>
<td>-31</td>
<td>110</td>
<td>0.000</td>
</tr>
<tr>
<td>Ec nod-mus</td>
<td>14.54</td>
<td>-70</td>
<td>100</td>
<td>0.010</td>
</tr>
</tbody>
</table>

\(^\S\)Mann Whitney.

Fig. 5: Box plots of muscle intensity (EL) stratified by age groups.

References: Department of Radiology, HFF
**Fig. 6:** Box plots of the difference between thyroid and muscle intensity (EL) stratified by age groups.

*References:* Department of Radiology, HFF
Fig. 7: Box plots of the difference between nodule and muscle intensity (EL) stratified by age groups.

References: Department of Radiology, HFF
**Fig. 8:** Box plots of muscle grey scale stratified by age groups.

**References:** Department of Radiology, HFF
Fig. 9: Box plots of the difference between thyroid and muscle grey scale stratified by age groups.

References: Department of Radiology, HFF
Statistically significant differences were found between the two age groups for the following variables: muscle intensity ($p=0.000$); intensity difference between the thyroid and the muscle as well as between the nodule and the muscle. There were no statistically significant differences in the two groups in what concerned thyroid intensity ($p = 0.174$) nor in intensity difference between the thyroid and nodule ($p = 0.422$).

The statistically significant results were the same in the second measurement method and concordant in the two measurement methods performed.
Fig. 11: age >60 years; grey scale measurement - osirix®

References: Department of Radiology, HFF
Fig. 12: age <60 years; grey scale measurement - osirix®

References: Department of Radiology, HFF
Fig. 13: age <60 years; intensity (EL) measurement GE logic E9
References: Department of Radiology, HFF

Fig. 14: age >60 years; intensity (EL) measurement GE logic E9
References: Department of Radiology, HFF
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Fig. 4: box plots of mean grey scale distribution - all nodules

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Fig. 5: Box plots of muscle intensity (EL) stratified by age groups.

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Fig. 6: Box plots of the difference between thyroid and muscle intensity (EL) stratified by age groups.

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Fig. 7: Box plots of the difference between nodule and muscle intensity (EL) stratified by age groups.

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**Fig. 8:** Box plots of muscle grey scale stratified by age groups.

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Fig. 9: Box plots of the difference between thyroid and muscle grey scale stratified by age groups.

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Fig. 10: Box plots of the difference between nodule and muscle grey scale stratified by age groups.

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**Fig. 11**: age >60 years; grey scale measurement - osirix®

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**Fig. 12:** age <60 years; grey scale measurement - osirix®

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**Fig. 13:** age <60 years; intensity (EL) measurement GE logic E9

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**Fig. 14:** age >60 years; intensity (EL) measurement GE logic E9

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Conclusion

Discussion:

Higher (less negative) echogenicity levels are associated with a more hyperechogenic structure.

Higher (more positive) grayscale values are associated with whiter structures.

Muscles tend to become less voluminous and undergo lipomatous infiltration as they age, which means they will be more hyperechogenic in ultrasound.

When forming two groups (one for individuals up to 60 years of age and the other for those older than 60) and either testing for echogenicity level or measuring grayscale values, we ascertain that the first of these groups shows statistically significant lower values when compared to the latter.

Since healthy thyroids are hyperechogenic, comparing the echogenicity of healthy thyroid parenchyma and muscle reveals a smaller (statistically significant) difference between the two structures' values in the older group's case.

Also, since most nodules are more hyperechogenic than muscles, the differences in echogenicity are lower and statistically significant in the older group for both measuring methods.

The thyroid's echogenicity is unaltered by age. As such, comparing its values between the two groups serves as a trustworthy control method for our measuring technique, the expected result being the absence of any statistically significant difference between them.

The same thought process can be applied to both the nodule echogenicity and difference between the nodule and thyroid's echogenicity variables.

This study was subject to a few limitations: the images were acquired and rated by a single radiologist; only one ultrasound display was used, with integrated EL measurement software. While simple to use, it is dependent on the used pre-set, namely the probe's frequency, which might not be reproducible in alternative equipment.

Analysing the grayscale implies saving the images in DICOM format, which is at once time-consuming and not always profitable.

We made sure to evaluate nodules pertaining to all kinds of echogenicities (as opposed to nothing but hypoechogenic nodules). Also, we did not exclude thyroids showing a diffuse change in echogenicity (thyroiditis) from our analysis.
In order to evaluate steatosis (8), echogenicity quantification (EL) in images has been performed for other organs, namely the liver. We found reference in the thyroid to the measuring of nodule echogenicity before and after ultrasound contrast. However, the difference between the basal value of benign and malignant nodules (9) was the only statistically significant result obtained.

To the best of our knowledge, a study similar to this one has yet to be performed.

We believe these findings possess clinical relevance, since the decision/assessment of which nodule to puncture is currently performed subjectively, comparing the nodule’s echogenicity with the normal thyroid and muscle. Seeing as that difference is lower in the older age group, it is possible we may be overvaluing "very hypoechoic" nodules in elder patients, with the reverse situation occurring within the younger group (in short, do not value a very hypoechoic nodule because the muscle is also very hypoechoic).

Maybe neck muscles aren’t the best reference standard for comparison with echogenicity of thyroid nodules. Or we need to consider patient’s age when performing this subjective comparison.

We believe a prospective study may be performed in the future, this time with several observers, making it possible to compare the subjective evaluation in the echogenicity relationship between hypoechoogenic nodules, healthy thyroid parenchyma and muscle, with ultrasound quantification (ideally performed on more than one equipment), for different age groups. Also, taking care to ascertain whether there is any relation between those observations and the nodules’ cytological/histological result.

**Conclusion**

In this study, we demonstrate that neck muscle echogenicity is different in different age groups, being less echogenic in the older group. We think this fact should be taken into account when selecting thyroid nodules for cytology.


