Role of quantitative diffusion-weighted MRI and 1H MR spectroscopy in distinguishing between benign and malignant thyroid nodules

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Purpose

Thyroid nodules are a common clinical entity; present in 4% to 7% of the general population.\(^{(1)}\) The vast majority of these nodules are benign, with only 5% of all solitary nodules proving to be malignant \(^{(2)}\).

While the vast majority of these lesions are benign follicular adenomas, the exclusion of thyroid malignancy remains a significant diagnostic problem \(^{(1)}\).

The history and physical examination remain the diagnostic cornerstones in evaluating the patient with a thyroid nodule and may be suggestive of thyroid carcinoma. A high index of clinical suspicion is contemplated when the following clinical features are present in an individual with euthyroid STN: rapidly growing hard or fixed nodule, with palpable neck nodes in central or lateral cervical compartments, with hoarseness of voice, or family history of thyroid cancer, or exposure of head and neck to radiation in childhood.\(^{(3)}\)

At present, we believe that fine needle aspiration cytology (FNAC) and ultrasound are the best method for investigating thyroid nodules. However, even in experienced hands there are cases in which the etiology of the nodule remains uncertain and surgery has to be performed for diagnostic purposes.\(^{(4)}\)

Cytology of biopsies obtained through fine-needle aspiration (FNA), the standard diagnostic modality for thyroid cancer, is unable to discriminate benign from malignant follicular thyroid nodules, which are differentiated only by capsular or vascular invasion. Therefore, many thyroidectomies are performed simply to exclude a diagnosis of malignancy.\(^{(5)}\)

In the benign case, the thyroid gland is unnecessarily removed solely for diagnostic purposes. *Ex vivo* proton MRS on resected tissue as well as on FNA has been reported to accurately discriminate malignant thyroid nodules from normal tissue.\(^{(6,7)}\)

Routine T1- and T2-weighted (W) magnetic resonance imaging (MRI) has a limited role in the evaluation of thyroid nodules and cannot assess the real functional status of thyroid nodules \(^{(8,9,10)}\)

In order to decrease the risk of unnecessary surgery, as well as the financial burden to the community, there is a need for a new non-invasive pre-surgical diagnostic test. At present proton magnetic resonance spectroscopy \(^{(1}H\text{ MRS})\) is being used to evaluate cancers in many regions of the body, but the neck poses many technical difficulties such as shimming and subject motion for in vivo spectroscopy.\(^{(5)}\)
In MR spectroscopy, Choline peak was specifically looked for. It was seen that presence or absence of choline peak correlates very well with presence or absence of malignant foci with in the nodule.\(^{(11)}\)

The choline peak at 3.22 ppm is predominantly due to glycerophosphocholine and glycerophosphoethanolamine that form phospholipids of the cell membranes. The choline content rises in malignancy because of rapid multiplication and proliferation of cells. Height of choline peak depends on amount and nature of tissue under voxel.\(^{(11,12)}\)

Diffusion Weighted Imaging (DWI) play an important role in differentiating benign or malignant nodules of the thyroid gland. Reduced ADC values have been reported for most malignant tumors and are thought to be due to cellular membranes impeding the mobility of water protons.\(^{(13-14)}\)

Standard treatments in some cases of advanced differentiated thyroid cancer and medullary thyroid cancer (radiotherapy and/or chemotherapy) have been unsatisfactory and therefore new therapies are necessary. In a near future, Tyrosine Kinase Inhibitors (TKIs) may open a new era in the radioactive iodine refractory DTC and advanced MTC patients treatment.\(^{(15)}\)

Numerous small molecule tyrosine kinase inhibitors have been developed and tested in a variety of tumor types. The success of these inhibitors hinges on the discovery of appropriate targets so integral in tumorigenesis that their disruption is catastrophic for the tumor.\(^{(16)}\) In thyroid cancer, the targets that have been best described include the RET/papillary thyroid carcinoma (PTC), RAS, and BRAF. Non-overlapping rearrangement of RET/PTC, and mutations of RAS, BRAF, and neurotrophic tyrosine kinase receptor 1 (NTRK1) have been found in w70% of PTC.\(^{(17)}\)

The objective of this study is to evaluate the role of combined quantitative diffusion MRI and MRS in differentiation between benign and malignant thyroid nodules.

**Methods and materials**

Approval of Research Ethics Committee (REC) of Tanta University and informed written consent were obtained from all participants in the study.

From February 2012 to May 2013, prospective study was conducted on 25 patients collected from wards and clinics of Internal Medicine and General Surgery Departments, with 41 thyroid nodules (11 male and 14 female, age range, 16-74 years with mean 45.3 years. 20 healthy individuals were included in the study as control group(9 males and 11 females age range, 20-65 years with mean 48 years). All individuals of the study were subjected to: full history taking, thorough clinical examination and routine laboratory
investigations in the form of: CBC, liver and kidney function test, fasting and 2 hours postprandial blood glucose, ESR, LDH, CRP, TSH.

All patients were subjected to: U/S on the neck, FNAB, histopathological examination of the nodules after surgical removal, preoperative 1.5-T $^1$H-MR Spectroscopy (at echo-times (TE) 144 and 35 ms) and diffusion-weighted imaging (b value 250 and 1000 s/mm$^2$).

All MR imaging and $^1$H-MRS studies were performed using a 1.5 T system (Signa; GE Medical Systems, Milwaukee, WI, USA) with neurovascular coil (NV array). The routine imaging studies included multiplanar T2-weighted fast spin-echo (4000/126/2) with an echo train length of 8 sequences.

**MR spectroscopy**

Optimal water resonance suppression was achieved. The parameters used were 2000/270, 192 acquisitions, a spectral width of 2500 Hz, and 2048 data points for all patients. In all patients, MR spectra were obtained with a TE of 144 with additional TE 35. The acquisition time for each sequence was 7 minutes 54 seconds.

Fast spin-echo images were transverse T2-weighted MR images. $^1$H-MRS was performed by a multivoxel long and short echo (TE, 144 & 35 ms) point-resolved spatially localized spectroscopy. The area of interest in all patients was the thyroid gland. The section thickness was 20 mm, and the anterior-to-posterior and right-to-left dimensions were 30 × 30 mm.

Metabolites of biologic importance, Choline (Cho) and Creatine (Cr) were detected by this technique.

The multivoxel MRS data were processed by the spectroscopic analysis package on the workstation. The resonances of main metabolites were quantified as follows: the Cr peak at 3.02 ppm, the Cho peak at 3.20 ppm, and the Lac doublet at 1.33 ppm.

The ratio of Cho/Cr was measured in cases with detected choline.

**Diffusion-Weighted Imaging and Apparent Diffusion Coefficient Mapping**

Diffusion-weighted imaging was performed in the transverse plane by using an SE echo-planar imaging sequence with the following parameters: TR/TE/TI (inversion time), 12000/95/2200 ms; diffusion gradient encoding in three orthogonal directions; b = 1000 and 250 s/mm$^2$; FOV, 24×40 cm; matrix size, 128×256 pixels; section thickness, 5 mm; section gap, 2.5 mm. An ADC map was obtained. In quantitative study, an imaging slice was chosen, five (1- to 2-cm) circular region of interest were located on the thyroid nodule/nodules, mean ADC value is calculated for benign and malignant nodules.

Twenty normal thyroid lobes of control patients were also evaluated for ADC values.
The sensitivity and the specificity of DWI, MR spectroscopy and both techniques are calculated.

The readers of the diffusion WI is blinded to the MRS results primarily.

Findings were compared with histopathology of thyroid specimens in all cases.

Statistical Analysis:

Statistical presentation and analysis of the present study was conducted, using the mean and standard deviation by SPSS V.16. Analysis of variance [ANOVA] tests and Tukey’s test was used to determine the significance between 2 groups: According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data. P value < 0.05 was considered significant.

Results

Prospective study was conducted on 25 patients (11 male, 14 female age range, 16-74 years with mean 45.3 years) and 20 healthy individuals control cases, 14 patients have single nodule, six patients have two nodules, 5 patients have 3 nodules with total 41 nodules, 28 nodules were benign (19 adenomatous nodules and 9 follicular adenoma), 13 nodules were malignant (eight papillary carcinomas, three follicular carcinoma, one medullary carcinoma, and one anaplastic carcinoma).

There were four cases with reactive lymph nodes and three cases of lymph node metastases from lymphoma, anaplastic carcinoma and medullary carcinoma, the metastatic lymph nodes characters were (The short axis diameter was more than 1cm, rounded, Blurred outline, Central degeneration (one case), heterogeneous enhancement in two cases and marginal enhancement in one case).

Descriptive characteristics of patients with thyroid nodules are shown in table1.

The mean ADC of the malignant thyroid nodules (13 nodules) were \((0.59 \pm 0.24 \times 10^{-3} \text{ mm}^2/\text{s})\) while that of the benign thyroid nodules (28 nodules) was \((1.78 \pm 0.21 \times 10^{-3} \text{ mm}^2/\text{s})\) (The difference between the mean ADC values of benign and malignant thyroid lesions was statistically significant (P<0.001). No statistically significant differences in ADC values among the different benign lesions or among the different malignant lesions at both sequences.). (Table 2)

The malignant thyroid nodules showed extremely low ADC value (< \(0.6 \times 10^{-3} \text{ mm2/sec}\) (9 nodules) (figure 1,2) and low ADC value (0.6 - <1.2 \(\times 10^{-3} \text{ mm2/sec}\) (4 nodules), while
benign nodules shows high ADC value ($>1.8 \times 10^{-3}$ mm$^2$/sec) (20 nodules) figure (3) and intermediate value (1.2 - $<1.8 \times 10^{-3}$ mm$^2$/sec ) (8 nodules) (figure 4).

Choline was present in all malignant nodules (13 nodules) (figure 1,2) and 2 benign nodules (figure 4) (can be explained by rapid turnover of cells in a hypeplastic nodule) while absent in 26 other benign nodules (figure 3) and 20 cases of control group. (Table 3).

The choline/creatine ratio of tumors with detectable choline peak (malignant nodules (n=13) and benign nodules (n=2) were shown in (table 4) (figure 1,2,4).

Comparison between combined (diffusion WI and MRS) and histopathological results were shown in (Table 5)

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of quantitative diffusion WI, MR spectroscopy and combined quantitative diffusion and MRS were shown in (table6).

Images for this section:
Table 1: Descriptive characteristics of patients with thyroid nodules (n = 25) and controls (n = 20)

<table>
<thead>
<tr>
<th>Character</th>
<th>Control (N=20)</th>
<th>Patients (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>M=9 F=11</td>
<td>M=11 F=14</td>
</tr>
<tr>
<td><strong>Age (range and mean)</strong></td>
<td>20–65 48</td>
<td>16–74 45.3</td>
</tr>
<tr>
<td><strong>TSH (uIU/ml)</strong></td>
<td>2.9±2.1</td>
<td>3.2±1.9</td>
</tr>
<tr>
<td><strong>ESR 1st hour mm</strong></td>
<td>7.625 ± 0.407</td>
<td>75.75 ± 2.285</td>
</tr>
<tr>
<td><strong>LDH (U/L)</strong></td>
<td>316.3 ± 14.69</td>
<td>398.1 ± 21.65</td>
</tr>
</tbody>
</table>

Table 1: Table 1: Descriptive characteristics of patients with thyroid nodules (n = 25) and controls (n = 20)

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Diffusion WI</th>
<th>Mean ADC value x 10⁻³mm²/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign nodules n=28</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular adenoma (n=9)</td>
<td>Mild restricted</td>
<td>1.76 ± 0.15</td>
</tr>
<tr>
<td>Adenomatous nodule (n=19)</td>
<td>diffusion</td>
<td>1.81 ± 0.27</td>
</tr>
<tr>
<td><strong>Tumors n=13</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma (n=8)</td>
<td>Restricted</td>
<td>0.63± 0.32</td>
</tr>
<tr>
<td>Follicular carcinoma (n=3)</td>
<td>diffusion</td>
<td>0.72 ± 0.17</td>
</tr>
<tr>
<td>Medullary carcinoma (n=1)</td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Anaplastic carcinoma (n=1)</td>
<td></td>
<td>0.45</td>
</tr>
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</table>
Table 2: Table 2: correlation of diffusion WI and ADC value with histopathological results

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Ch/Cr ratio</th>
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</thead>
<tbody>
<tr>
<td>Follicular adenoma (n=2)</td>
<td>0.9, 1.1</td>
</tr>
<tr>
<td>Papillary carcinoma (n=8)</td>
<td>3 ± 1.7</td>
</tr>
<tr>
<td>Follicular carcinoma (n=3)</td>
<td>3.5 ± 2.1</td>
</tr>
<tr>
<td>Medullary carcinoma (n=1)</td>
<td>5.4</td>
</tr>
<tr>
<td>Anaplastic carcinoma (n=1)</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4: Table 4: correlation between choline/creatine ratio and histopathological results.

<table>
<thead>
<tr>
<th></th>
<th>Diffusion WI and MRS</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>malignant</td>
</tr>
<tr>
<td>Benign nodules (n=28)</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Malignant nodules (n=13)</td>
<td>-</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 5: Table 5: correlation between combined Diffusion WI and MRS and histopathological results:

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>MRS</td>
<td>96</td>
<td>85</td>
<td>92</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Quantitative diffusion</td>
<td>96</td>
<td>92</td>
<td>96</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>Diffusion and MRS</td>
<td>100</td>
<td>93</td>
<td>96</td>
<td>100</td>
<td>97</td>
</tr>
</tbody>
</table>

Table 6: Table 6: sensitivity, specificity, PPV, NPV and accuracy of MRS, diffusion study and combined techniques:

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Benign (28)</td>
</tr>
<tr>
<td>Choline peak present</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Choline peak absent</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>
**Table 3:** Table 3: correlation of choline peak with histopathological results:

**Fig. 1:** Fig. 1 (a-d): Papillary carcinoma of the thyroid. Female patients aged 55-year old complaining of painless swelling in almost midline part of the neck, difficulty in breathing. MRI: shows evidence of 2 well defined homogenously nodules-seen in isthmus of thyroid gland (in infrahyoid visceral neck space) displaying high SI on T2 WI. Diffusion study revealed: the thyroid isthmus mass shows restricted diffusion in DWI, mean ADC value =0.4 - 103 mm2/s (extremely low ADC). MR spectroscopy: revealed choline peak at 3.2 ppm with choline/ creatine ratio 1.5. (a) Axial T2; (b) diffusion WI; (c) ADC map; (d) MR spectroscopy.
Fig. 2: Follicular thyroid carcinoma. Female patients aged 28 years complaining of painful swelling in middle and left side of neck, difficulty in swallowing and hoarseness of voice. MRI: shows enlarged both thyroid lobes with large left thyroid lobe lobulated mass hanging down reaching to the level of suprasternal notch (in infrahyoid visceral neck space), displaying mild heterogeneous SI in T2WI with areas of high SI denoting cystic changes. Diffusion study revealed: restricted diffusion in DWI. Mean ADC value = 0.1 · 103 mm2/s (extremely low ADC). MR spectroscopy: revealed choline peak at 3.2 ppm with choline/creatine ratio 1.7. (a) Axial T2; (b) diffusion WI; (c) ADC map; (d) MR spectroscopy.
Fig. 3: Thyroid nodules with Hashimoto’s thyroiditis. Female patient aged 20 years complaining of painless swelling in midline of the neck. MRI: shows diffuse enlargement in both thyroid lobes (in infrahyoid visceral space of the neck), with multiple bilateral ill-defined thyroid nodules displaying hyperintense SI in T2 WI. Diffusion study revealed: bilateral areas of mild restricted diffusion in DWI. Mean ADC value = 2.6 · 103 mm2/s (high ADC). MR spectroscopy: absence of choline peak denoting benign nodule. (a) Axial T2; (b) diffusion WI; (c) ADC map; (d) MR spectroscopy.
Fig. 4: Fig. 4 (a-d): A typical thyroid nodule: Male patient aged 30 years complaining of painless swelling in right side of the neck. MRI: shows right thyroid nodule (in infrahyoid visceral space of the neck) displaying hyperintense SI in T2 WI. Diffusion study revealed: Reveal restricted diffusion in DWI. Mean ADC value = 1.7 · 103 mm2/s (intermediate ADC). MR spectroscopy: mild choline peak, choline/ creatine ratio 1.1. The patient repeat FNAC after 4 months and no malignancy revealed. (a) Axial T2; (b) diffusion WI; (c) ADC map; (d)MR spectroscopy.
Conclusion

Thyroid nodules are the most common disorders of thyroid gland, more common with increasing age and more frequent in women; only 3%-5% of all nodules are malignant. (1, 18)

Diffusion-weighted MR imaging has been used to characterize head and neck tumors, in which there are significant differences in the apparent diffusion coefficient (ADC) values of malignant tumors and benign lesions. (19, 20)

In this study, the mean ADC of the malignant thyroid nodules (13 nodules) was \(0.59 \pm 0.24 \times 10^{-3} \text{mm}^2/\text{s}\) while that of the benign thyroid nodules (28 nodules) was \(1.78 \pm 0.21 \times 10^{-3} \text{mm}^2/\text{s}\) (significant p value <0.0001). This is in agreement with the study of El-Hariri et al (21) who studied on 46 patients with 56 thyroid nodules as the mean ADC of the benign thyroid nodules in their results was \(1.85 \pm 0.24 \times 10^{-3} \text{mm}^2/\text{s}\) while the mean ADC of the malignant thyroid nodules was \(0.89 \pm 0.27 \times 10^{-3} \text{mm}^2/\text{s}\). The ADC values of malignant thyroid nodules were significantly lower than the ADC values of benign thyroid nodules (p value <0.0001).

In the study of Abdel Razek A. et al (8) the ADC value of \(0.98 \times 10^{-3} \text{mm}^2/\text{s}\) was the cutoff value differentiating between benign and malignant nodules while in our study the cutoff value was \(0.8 \times 10^{-3} \text{mm}^2/\text{s}\) as highly cellular adenomatous tissue shows slight low ADC value.

In this study we use b value 0, 250 and 1000 in diffusion imaging while in the study of Abdel Razek A. et al (8) who use b-values of 0, 250, and 500 s/mm² and they Suffice with them to obtained high image quality and a high sensitivity for diagnosis of thyroid cancer while the use of higher b value reflecting the true diffusion of the tissue.

The study of gupta et al (11) who studied on MRS of thyroid carcinoma reported that of the 17 benign cases of benign thyroid nodules, only 1 showed choline peak; however, all 8 follicular carcinoma cases showed prominent choline peak. Hence, the sensitivity is 100% while the specificity is 94.11% this is nearly coincide with our results as 2 out of 28 cases of benign thyroid nodules show mild choline peak in MR spectroscopy but not coincide with them in the statistical analysis as the sensitivity of MRS in this study was 96% while the specificity was 85%.

Elevated Cho is detected in thyroid carcinomas but not in normal thyroid tissue. Creatine also can be detected frequently in malignant lesions allowing calculation of Cho/Cr ratios, which in this study ranged from 1.3 to 5.6 in malignant thyroid nodules, this coinciding with the results of Aydin H. et al 2012 (22) that study on The role of proton
MR spectroscopy and apparent diffusion coefficient values in the diagnosis of malignant thyroid nodules, their results conclude that Cho/Cr ratio for the malignant nodules was 2.95±1.54 - 5.30±2.38.

FNA biopsy remains the gold standard for evaluating thyroid nodules. Most clinical practice guidelines recommend FNA biopsy for nodules measuring greater than 1 cm in largest dimension.\(^{(23)}\)

The false-negative rate for FNA biopsy is 1% to 3%. The false-negative rate increases to 10% to 15% when the nodule is large (>4cm).\(^{(24)}\)

To determine whether nodules with indeterminate cytology on FNAB (follicular neoplasm, atypia, etc) are benign or malignant without the need for diagnostic surgery, Nikiforov et al recently developed a panel of mutations including BRAF, NRAS, HRAS, KRAS, and 2 different RET/PTC rearrangements. The detection of any one of these mutations was associated with a final histopathologic diagnosis of cancer in 88% of cases with a cytologic diagnosis of atypia and 87% of cases with cytologic diagnoses of follicular neoplasm/suspicious for a follicular neoplasm.\(^{(24)}\)

Limitation of this study are in motions artifacts by movement of the tumor as a result of swallowing and breathing, magnetic susceptibility differences between air in the trachea, bone and thyroid tissues and contamination of the voxel by adjacent fat.

Also the limitation in this study is the small number of malignant cases which decrease the statistical strength.

**CONCLUSION:**

Combined MRS and diffusion WI are useful noninvasive diagnostic modalities for differentiating between benign and malignant thyroid nodules with excellent results that could be used instead of FNAB and avoid unuseful thyroidectomy to exclude malignancy. Elevation of choline and low ADC value can diagnose malignant thyroid nodules but cannot differentiate between different types of malignant neoplasm.

**Personal information**

Rasha Elshafey

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