Comparison of thyroid fine needle aspiration biopsy results and efficiency of diffusion-weighted MRI in differenciating malignant and bening thyroid nodules

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Purpose

Thyroid nodules are frequent lesions of thyroid and some of them are difficult to recognize without ultrasonography (US). Prevalance of thyroid nodules approaches to 50% in postmortem studies. Thyroid scintigraphy and ultrasonography are commonly used for the diagnosis of thyroid nodules. Although there are some ultrasonographic criteria (i.e. Hypoechogenity, microcalcifications, thick and irregular halo, lymphadenopathies, increased internal Doppler flow) for differentiation of malignant and benign nodules, none of these criteria has high sensitivity or specificity alone. Fine-needle aspiration biopsy (FNAB) gives more valuable information and it is gold-standart for nodule evaluation with 83% sensitivity and 92% specificity (1). Diffusion-weighted imaging (DWI) has been used for Graves' disease and Hashimoto's thyroiditis and the apperent diffusion coefficient ( ADC ) values of the patients with Graves disease were significantly higher than other (2). In two different studies searching ADC values in malignant and benign solid nodules, ADC values were significantly lower in malignant nodules and they were correlated with histopathological evaluation (3,4). In our study we aimed to evaluate the eff#ciency of diffusion-weighted imaging (DWI) to compare its results with FNAB evaluation of nodules, and to evaluate ADC values of normal-appearing thyroid paranchyme in normal healthy controls and patients with thyroid nodules.
Methods and Materials

Groups and patients: We enrolled 96 patients (57 women, 39 men) into the study. All patients were between 18-65 years of age and all patients had informed consent. Patients without heterogenous paranchyme on US (i.e. probable thyroiditis), pure cystic nodules, nodule size > 1.5 cm and without any contraindication of MRI were grouped as Group 1. There were 56 patients (42 women, 14 men) in Group 1 and they had first DWI and then FNAB. Forty patients without thyroid nodules (25 men, 15 women with mean age =44.7±8.8 years) were enrolled as controls, as Group 2, and they only had DWI.

Radiologic methods: Thyroid ultrasonography examinations were performed by LOGIQ 7 (GE Medikal Sistem, Milwaukee, WI, USA) with 10 MHz probe. DWI evaluations were performed by 1.5 T MRI (General Electric, Signa, Milwaukee, WI, USA) with head and neck coil, with axial sequential plans. In conventional MRI, our protocol was T1-weighted FSE sequences (TR=532 msec, TE=15 msec) and T2-weighed FSE sequence (TR/TE=4100/102 msec), FOV=24x24 cm; section thickness=4 mm; excitation number=2 ve intersection gap= 0 . In DWI, using b factors of 100,200, 300 "single shot" spin echo and EPI sequences were accepted. We preferred lower b factors that may cause less artefacts with smaller lesions since higher values may cause distortion and low quality of images although they may provide more information about diffusion features. Parameters for DWI were; TR = 1000 ms; TE = minimum; FOV= 24x24 cm; excitation number =2; acquisition matrix# 128 x 128; section thickness = 4 mm; intersection gap = 0 and time=40 s. We had T1W and T2W images and DWI from the same part of the thyroid tissue to evaluate the signal characteristics of the nodule. Since ADC measurement of the cystic part of the nodule may cause overestimated ADC values it was performed from solid part. Region of interest (ROI) was placed to solid component of the nodule or solid-cystic border or normal thyroid by the help of US evaluation (Figure 1).

All measurements were repeated by 3 different b factors. Mean ADC values were calculated for lesions and compared for nodules with benign and malignant FNAB results. Meanwhile, ADC values of normal paranchymes of patients with thyroid nodules patients were compared with Group 2 and nodulary and normal areas of thyroid of Group 1. FNAB: All FNABs were performed as US-guided. Three specimens were taken from each nodule from different sites within the nodule ,by sterile 10 cc 22G injection needle, considering both solid and cystic components.
Cytopathologist was evaluated each specimen and results were categorized as malignant, benign, suspicious and insufficient (Figure 2,3).

Statistical methods: Statistical analyses were performed by "SPSS for Windows Version 15.0" program. Variables were listed as mean±standard deviation and median values. Comparison of benign, malignant and healthy groups were done by Kruskal Wallis ve Mann Whitney tests. Paranchyme- nodule comparisons of benign and malignant groups were performed by Wilcoxon test and t-test. Values separating benign and malignant groups according to the b factors was calculated by receiver operating characteristic (ROC) curve analyses (Statistical significance was accepted as p<0.05).
Fig. 0: Figure 1: Normal thyroid gland in twenty five year old woman. A. Axial T1W image. B. Axial T2W image. C. Axial US image. D. Using b 300 factor in the axial color ADC map, ADC values were obtained from both of the lobes. The value obtained from right lobe 1.70 x 10^{-3}, from the left lobe 1.87 x 10^{-3} mm²/sec.

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Fig. 2: Benign follicular nodule of the thyroid gland in the superior of the left lobe in a forty two year old female patient. A. In the axial US image, iso-hypoechoic solid nodule that shows cystic degeneration areas is seen. B. In the axial T2W image, heterogeneous hyperechoic nodule is seen. C. In the color ADC map (b factor:300), ADC value obtained from the nodule $1.18 \times 10^{-3} \text{mm}^2/\text{sec}$. D. In the cytology of the follicular nodule, colloidal areas and thyroid cell groups were evident (Giemsa staining, x 20).

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Fig. 3: Papillary carcinoma of thyroid gland in the inferior pole of right lobe in a sixty three year male patient. A. In the axial US image, iso-hypoechoic solid nodule that has hypoechoic area surrounded by a thick halo is seen. B. In the axial T2W image, heterogeneous hyperechoic nodule is seen. C. In the color ADC map (b factor:300), ADC value obtained from the nodule $0.46 \times 10^{-3} \text{mm}^2/\text{sec}$. D. In the cytology of the papillary carcinoma; besides cell groups that formed papillary structure, tumor cells that had intranuclear inclusion bodies were seen as well (Giemsa staining, x 60).

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Results

We found 56 of the patients as having nodular thyroid disease with nodules with largest diameter>1.5 cm, without pure cystic nodule structure and without thyroiditis-related echogenity in paranchyme by US evaluation (Group 1). Forty patients with normal US were included into Group 2. Group 1 patients were 75% females and 25% males (mean age=44.5±10.42 years), and there were 70 thyroid nodules in this group. FNAB results of these nodules were: 59 nodules (%84.285) benign, 6 nodules (%8.571) malignant and 5 nodules (% 7.142) suspicious. Patients with suspicious nodules were excluded from study. FNAB of 4 nodules were non-diagnostic and when repeated they also revealed benign and included into benign group. Mean nodule size was 23.8±0.53 mm Group 2 was consisting of 40 patients with ultrasonographically normal thyroid glands. These patients were %62.5 females and % 37.5 males (mean age: 44.67±8.83 years). When demographic features of two groups were compared, only statistical significant difference was gender (p=0.001), in Group 1 there were more females. Table 1 shows the range and mean of ADC values of benign and malign nodules. Statistical differences between ADC values of malignant and benign nodules were significant (p=0.001) for all three b factors (Table 2). When we compared the ADC values of normal paranchymes of Group 1 and 2, there were no significant difference between two groups regarding any b factors (p values; for b-100 was p=0.10, for b-200 p=0.14, and for b-300 p=0.382) (Table 3).

We also compared ADC values of nodule and normal paranchyme of patients with thyroid nodules. There were no difference between intra- and extra-nodular ADC for any three b factors in patients with benign nodules (p values; for b-100 p=0.06, for b-200 p=0.16, and for b-300 p=0.75). Whereas in patients with malignant nodules intra- and extra-nodular ADC values were significantly different for all b factors (p values; for b-100 p=0.027, for b-200 p=0.046 and for b-300 p=0.027). Malignant nodules had lower b values compared to paranchyme.
Table 1: The range and mean of ADC values of thyroid nodules (x10^{-3} mm^2/sec).

<table>
<thead>
<tr>
<th>NODULE TYPE</th>
<th>NUMBER OF NODULES</th>
<th>RANGE OF ADC VALUES</th>
<th>MEAN ADC VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>b-100</td>
<td>b-200</td>
</tr>
<tr>
<td>Benign</td>
<td>59</td>
<td>1.39-4</td>
<td>0.72-3.19</td>
</tr>
<tr>
<td>Malignant</td>
<td>8</td>
<td>0.39-2.04</td>
<td>0.15-1.28</td>
</tr>
</tbody>
</table>

Fig. 0: Table 1: The range and mean of ADC values of thyroid nodules (x10^{-3} mm2/sec).

Tab. 2: In the discrimination of thyroid nodules as benign or malignant with three different b factors of ADC values; cut-off values, %95 confidence intervals (CI), area under curve (AUC), sensitivity, specificity and p values.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>b-100</th>
<th>b-200</th>
<th>b-300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut-off values</td>
<td>0.70</td>
<td>0.85</td>
<td>0.95</td>
</tr>
<tr>
<td>%95 CI</td>
<td>0.98-1.009</td>
<td>0.980-1.009</td>
<td>0.988-1.006</td>
</tr>
<tr>
<td>AUC</td>
<td>0.994</td>
<td>0.992</td>
<td>0.997</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Specificity</td>
<td>93</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>p-value</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. 0: Table 2: In the discrimination of thyroid nodules as benign or malignant with three different b factors of ADC values; cut-off values, %95 confidence intervals (CI), area under curve (AUC), sensitivity, specificity and p values.
Tab. 3: The mean ADC values of normal-appearing parenchyma of the cases with and without nodules (x10^-3 mm²/sec).

<table>
<thead>
<tr>
<th>b-factors</th>
<th>Mean ADC values of normal-appearing parenchyma</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>Malignant</td>
<td>Without Nodules</td>
</tr>
<tr>
<td>b-100</td>
<td>2.98±0.19</td>
<td>2.71±0.38</td>
<td>2.94±0.2</td>
</tr>
<tr>
<td>b-200</td>
<td>1.77±0.24</td>
<td>1.57±0.42</td>
<td>1.70±0.22</td>
</tr>
<tr>
<td>b-300</td>
<td>1.59±0.18</td>
<td>1.21±0.3</td>
<td>1.22±0.18</td>
</tr>
</tbody>
</table>

Fig. 0: Table 3: The mean ADC values of normal-appearing parenchyma of the cases with and without nodules (x10^-3 mm²/sec).
Conclusion

The target of thyroid nodular disease management should be to rule out the malignancy with 5-10% prevalence (5). Thyroid cancers constitute only 1% of all adult malignancies. Since they have better prognosis and slow progression, early diagnosis is important. Among physical examination, evaluation of patients detailed story with risk factors, thyroid function tests, radiologic imaging methods and FNAB are important tools. Although FNAB is still the gold-standart method for differentiation of malignant and benign nodules, non-diagnostic results may occur due to low cooperation of the patient, location and size of the nodule, and experience of the practitioner and cytopathologist. Although it is minimal invasive, it also may have local complications. Meanwhile, evaluation of only the dominant nodule is not enough, other nodules should also be evaluated and sometimes benign nodules may necessitate need for re-biopsy. Thus, alternative less invasive methods to evaluate thyroid nodules is required in such cases. In medical literature the knowledge about the use of DWI in thyroid nodules is still scarce and discordant. Weidekamm et al had compared postoperative pathology results and DWI with b-800 factor in cold nodules (6,7). In this study they had found that malignant nodules had higher ADC values than adenomas. They explained this result as that since the intracellular content depends on thyroglobulin production by follicules, this does not restrict diffusion capacity. In the study of Razek et al, DWI values with b-0, b-250 and b-500 factors of 67 cases were compared with FNAB results and they found malignant nodules with lower ADC values (3). Similar results were also obtained in the study of Bozgeyik et al with b-100, b-200 and b-300 (4). Our results were also in concordant with the results of these two studies, showing that malignant nodules have lower ADC values compared to benign nodules.

In our study, ADC values of intra- and extra-nodular areas were also compared. We found no significant difference between nodule and paranchyme in thyroids with benign nodules, whereas the ADC values were lower in malignant nodules compared with paranchyme. This could be explained by increased cellularity in malignant nodules. The absence of ADC values difference between paranchymal sites of Group 1 and Group 2 may be explained by the absence of relationship between primary pathology and normal-appearing thyroid paranchyme in these patients. Meanwhile, our study has some limitations. First, frequency of malignant nodules were low (9.23%) and this restricts statistical power. And all these malignant nodules were papillary thyroid carcinoma, therefore it was not possible to evaluate different cancer types in this study. Another restriction was exclusion of nodules lower than 1.5 cm diameter. In the future probable technological developments in the softwares of DWI may provide the evaluation of smaller
nODULES. Last, we did not included thyroid nodules with parenchymal appearance with chronic thyroiditis, to evaluate the normal pranchyme with intra-nodular area. But, it is known that patients with Hashimoto’s thyroiditis higher risk for thyroid cancers and we cannot conclude about this group of patients. Despite these restrictions, our study showed that DWI is a non-invasive method that may be used to differentiate benign and malignant thyroid nodules, but still larger studies with different thyroid cancers and thyroid parenchymal diseases must be performed to compare with FNAB. DWI may be a promising alternative method especially for the patients who need repeated FNAB, patients with multinodular thyroid disease that necessitates multiple FNABs, nondiagnostic FNAB results or uncooperated patients, to decrease need for biopsies.
References


