ORIGINAL RESEARCH

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ADC Values in Distinction of Benign and Malignant Thyroid Nodules

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ABSTRACT Objective: The additive of conventional magnetic resonance imaging (MRI) is evaluating the deep placed nodules and presence of distant metastases where USG might remain insufficient. DWI is noninvasive modality without using ionizing radiation and may differentiate benign and malignant nodules. **Material and Methods:** We prospectively evaluated 47 patients who demonstrated solitary thyroid nodules on ultrasonographic examination and underwent DWI of the thyroid gland. Apparent diffusion coefficient (ADC) values of these nodules were calculated and compared to histopathology results obtained with surgery. Whether a distinction for malignanvy nodules could be achieved by using mean ADC values were evaluated by statistical analysis. **Results:** The mean ADC values of malignant thyroid nodules were lower than benign nodules and the difference was statistically significant. ($p < 0.01$). There were also statistically significant differences between the ADC values of benign thyroid nodules of different types ($p < 0.05$). When a mean ADC cut off value of 1.81×10^{-3} mm^2 / sn was used in predicting malignancy, a 85.7 % sensitivity, 69.7 % specificity and 74.47 % accuracy were obtained. **Conclusion:** Since the mean ADC values of malignant thyroid nodules differs lower than benign nodules, DWI may be used to differentiate benign to malignant nodules.

Keywords: Diffusion magnetic resonance imaging; thyroid neoplasms

The prevalence of the thyroid nodules in general population is fairly high. They can be detected with manual palpation in 4% - 7%.[1,2] On ultrasound examination (USG) in 10% - 40%, and by pathological examination at autopsy in 50%.[3,4] Thyroid nodules are more frequently seen in adults and women.[5] Their importance is primarily related to necessity of excluding a thyroid malignancy.[6] Fortunately, compared with high prevalence of thyroid nodules, malignancy is rare.

In recent studies USG characteristics were evaluated in terms of potential feature of thyroid cancers.[7,8] In spite of presence of well known sonographic data, there is still an overlap in the appearance of these features.[8,9] Nuclear scintigraphy has risk of radiation exposure and not all hot or hyperfunctioning nodules detected on scintigraphy are benign.[10,11] Malignancy risk for cold nodule is four times more common compared with a hot nodüle.[3,10]

The importance of conventional magnetic resonance imaging (MRI) is evaluating the deep placed nodules and presence of distant metastases where USG might remain insufficient. DWI can contribute to determine nodule's malignancy potential.[12,13] Signal characteristics of benign and malign tissues differ on DWI. Additionally apparent diffusion coefficient (ADC) values quantitetively evaluates those differences. The ADC values objectively reflects the tissue-specific diffusion capacity.

The aim of our study was to evaluate the role of ADC values in the differentiation of benign and malignant thyroid nodules using histopathological results obtained with surgery as a reference standard.

MATERIAL AND METHODS

We designed a prospective study between March 2012 and April 2013 consisting of 47 patients with sonographically detected thyroid nodules. There were 37 women (78.7%) and 10 men (21.3%) patients and their mean age was found as 51.7 ± 14 years (age range 29-75 years).

This study was approved by our Instutitional Research Ethics Committee and informed consents were obtained from all patients prior to the study.

Solid and cystic thyroid nodules were included without exception.

Eight of patients who presented with severe motion artifacts and-or bad image quality were excluded from the study. Biopsy was not performed before MRI examination to avoid a distortion of ADC measurements arising from hemorrhage or susceptibility artifacts. We also selected thyroid nodules larger than 1 cm in size on USG examination for further evaluation with DWI. The reason we rejected thyroid nodules under this size was that they could not be evaluated by DWI due to subsequent low image quality. All patients were subjected to surgery following MRI and histopatho logical results were obtained from all thyroid nodules and served as the reference standard for evaluating the diagnostic value of DWI. Finally 47 solitary thyroid nodules were evaluated by DWI in order to differentiate between the benign and malignant nodules by using ADC measurements.

MRI technique: All examinations were performed by means of a 1.5 tesla superconducting magnet with high speed gradients (Signa Excite, GE Medical Systems, Milwaukee, Wisconsin, USA). A dedicated head and neck coil was used.

All patients underwent conventional T1 (TR: 600 ms, TE: 15 ms) and T2 weighted (TR: 4000 ms, TE: 106 ms) imaging.

Section thickness was 5 mm, and the intersection gap 1 mm,

FOV was chosen as 25 cm and an acquisition matrix was 256 x 256.

All images were obtained in the axial plane. We then performed diffusion - weighted ingle - shot spin- echo echo - planar sequence with chemical shift selective fat saturation technique under free breathing. A set of multiple axial images of the neck was obtained to cover the entire thyroid gland with the following imaging parameter. TR: 8000 ms, TE: 95.1 ms, matrix 128 x 128, FOV 16 cm, section thickness 5 mm, space 0 mm, number of excitations 2, parallel imaging factor 2, acquisition time 3.04 sec. The diffusion gradients were applied in three orthogonal directions (X, Y and Z). DWI was acquired with a diffusion factor (b factor) of 0 and 1000 s / mm² in this study.

Image analysis: Two 4 and 5 years of experienced radiologists who were blinded to the final cytology results evaluated T1, T2 and diffusion - weighted MR images and determined by consensus whether or not they had optimal quality for further evaluation. First, T1 and T2 weighted images were evaluated for detection and signal intensity characteristics of the thyroid nodules. Additionally, on T2 weighted images, the nodule size was measured, and then the DW images were transferred to a separate workstation (Advantage Windows, version 4.2, GE Medical Systems) where ADC maps were reconstructed using commercially avaliable software. A circular region of interest (ROI) was manually placed on the ADC map of nodules where they had greater dimensions and corresponding ADC values were measured. Calculated ADC values were expressed in square milimeters per second ($x\ 10^{-3}\ mm^2 / s$). We performed multiple ADC measurements to confirm the reproducibility of these values. We avoided covering the cystic part of the nodules in order not to have a falsely elevated ADC value and identified the cystic portions using baseline T1 and T2 weighted MR images. Mean ADC values of all thyroid nodules were calculated with a b value of 0 and 1000 s / mm^2. These ADC values were compared between benign and malignant nodules with histopathology results obtained by surgery being regarded as reference standard.

Statistical analysis: Statistical analysis was performed with NCSS (Number Cruncher Statistical System, 2007) and PASS (Power Analysis and Sample Size, 2008) statistic software (Utah, USA). Student - t test and chi square test were used to evaluate distribution of benign and malignant lesions related to age and sex, respectively. ADC values of benign and malignant lesions were compared using the student - t test. Comparison of ADC values between benign nodules was performed by the Kruskal Walli test and for pairwise comparisons a Mann - Whitney U test was used. Receiver operating characteristic (ROC) curve analysis was performed and a cut off value, sensitivity and specificity levels were calculated. A p value of < 0. 05 was considered as indicating a statistically significant difference.

Ethical statement: This study was approved by the appropriate ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

RESULTS

These nodules consisted of 33 (70.2%) benign and 14 (29.8%) malignant ones. Histopathological diagnoses of these nodules were as follows:

7 patients (14.9%) had adenomatous nodules, 9 patients (19.1 %) had benign follicular nodules, 6 patients (12.8%) had hyperplastic nodules,11 patients (23.4%) had colloidal nodules; 1 patient (2.1%) had follicular carcinoma, 2 patients (4.3%) had anaplastic carcinoma and 11 patients (23.4%) had papillary carcinoma.

The size of the thyroid nodules ranged from 10 to 37 mm (mean: 19.97±9.31 mm). A statistically significant difference was not found in relation to the age distribution of benign and malignant thyroid nodules ($p > 0.05$). A statistically significant difference was also not present in relation to the sex distribution of nodules ($p > 0.05$).

The range of ADC values in benign and malignant nodules were found as (1.31-2.80 x 10^{-3} mm^2 / s) and (1.27-2.20 x 10^{-3} mm^2 /s), respectively. The mean ADC values of benign thyroid nodules (2.11±0.41 x 10^{-3} mm^2 / s) were found significantly higher than those of malignant ones (1.55±0.31 x 10^{-3} mm^2 / s), despite the overlapping in some cases. This difference was found statistically significant. ($p < 0.01$). (Table 1) There were also statistically significant differences between the ADC values of different type benign thyroid nodules ($p < 0.05$) (Table 2).

The mean ADC values of adenomatous nodules (1.84 ±0.20) were found to be significantly lower than those of benign follicular nodules (2.43 ± 0.38) and colloidal nodules (2.30 ± 0.24) (p= 0.008, p = 0.001, $p < 0.01$). Benign follicular nodules had significantly higher ADC values (2.43 ± 0.38) than the hyperplastic ones (1.64±0.22) (p= 0.007, p < 0.01). A box plot illustrates the range of ADC values for benign and malignant thyroid nodules (Figure 1).

We also performed a ROC analysis to obtain a cut off ADC value in order to differentiate between benign and malignant thyroid nodules (Figure 2).

The area under the curve (AUC) was calculated as 0.857. We determined a cut off value of 1.81 x 10^{-3} mm^2 / s which yielded a 85.7% sensi-

TABLE 1: Evaluation of ADC values related to diagnosis

	Mean ADC	ADC standard dev.	p
Benign	2.11	0.41	
Malignant	1.55	0,31	<0.01

TABLE 2: ADC values of different type benign and malignant nodules.

	Diagnosis	N	Mean	SD	Median
Benign	Adenomatous nodule	7	1.84	0.20	1.79
	Benign follicular nodule	9	2.43	0.38	2.51
	Colloidal nodule	11	2.3	0.24	1.67
	Hyperplastic nodule	6	1.64	0.22	2.31
	Total	33	2.11	0.41	2.20
Malignant	Anaplastic ca	2	1.62	0.21	1.62
	Follicular ca	1	1.52		1.52
	Papillary ca	11	1.54	0.35	1.52
	Total	14	1.55	0.31	1.52

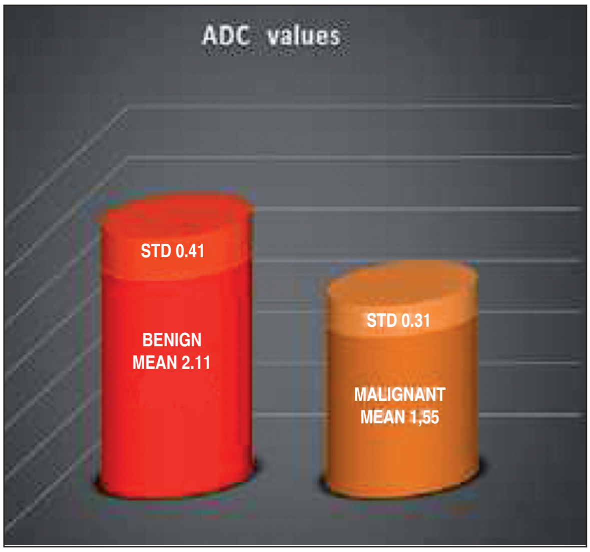

FIGURE 1: ADC values for benign and malignant thyroid nodules.

tivity, 69.7 % specificity, and 74.47% accuracy. The representative cases are shown in Figures 3-4.

DISCUSSION

The thyroid nodules can be defined as discrete lesions distinguishable from the normal parenchyma. They are more common in elderly patients and among women. Their lifetime risk to be seen is reported around 15 %. Most coomonly found benign nodules are adenomatous nodules and the remaining of them can be counted as adenomas, cysts and thyroiditis.[2,4,8,10] The frequency of malignant thyroid nodules relatively low and reported around 5%. In our study, the incidence of benign nodules was 70.2% and those of malignant ones was 29.8 %. Despite the fact that the majority of thyroid nodule turning out to be benign, the malignant

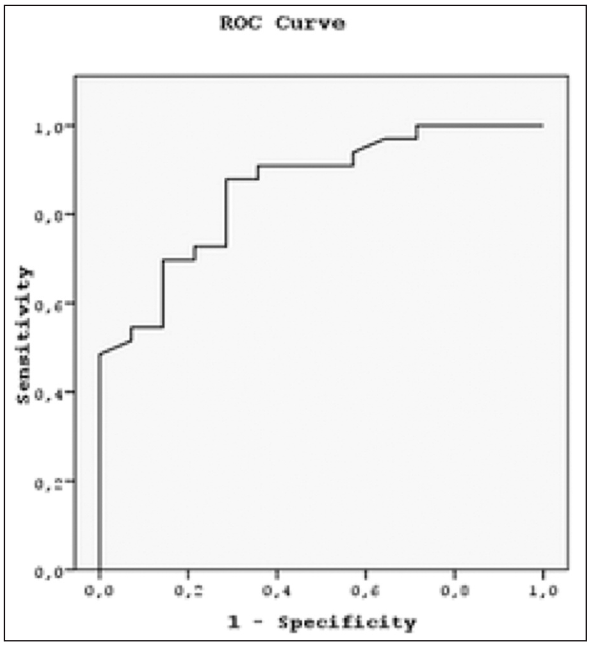

FIGURE 2: Receiver operating characteristic (ROC) curve of the ADC values for differentiation of benign and malignant thyroid nodules. The area under the curve (AUC) is 0.857.

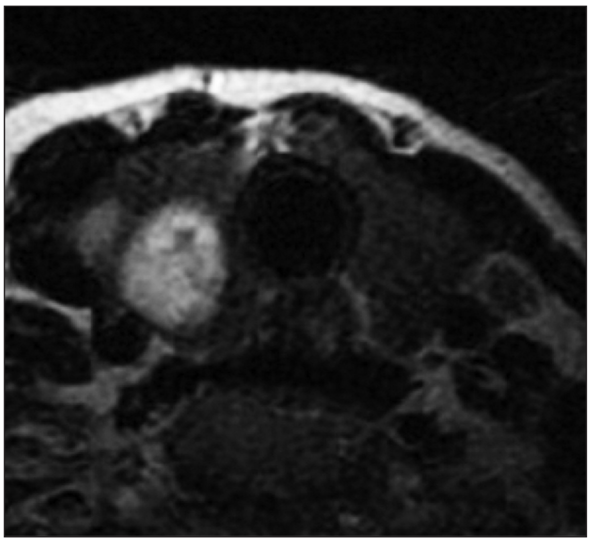

FIGURE 3: A 66 year-old woman with a 21 x 17 mm benign follicular nodule in right thyroid lobe. Axial T2 weighted MR image demonstrates high signal intensity nodule. ADC map calculated as 2.62 ± 0.58 x 10^{-3} mm² / s.

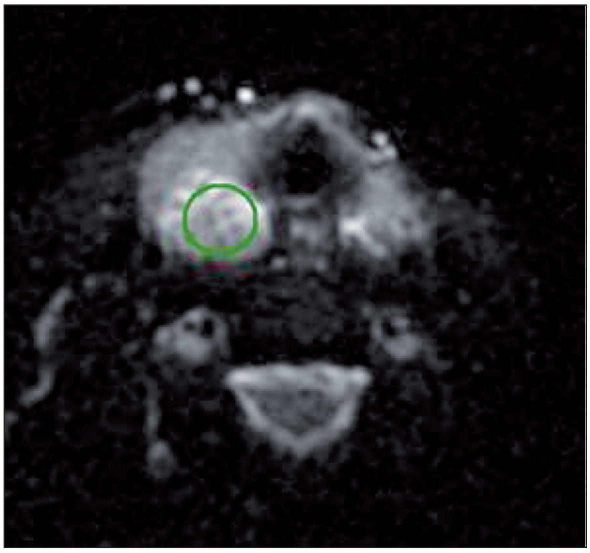

FIGURE 4: A 60 year-old woman presenting with a 28 x 19 mm papillary carcinoma in right thyroid lobe. Axial DWI reveals restricted diffusion in the nodule. ADC map reveals low signal intensity and was calculated as 2.20 ± 0.18 x 10^{-3} mm^2 / s.

thyroid nodules should not be overlooked by their characteristic imaging findings.

The aim of evaluating a thyroid nodule is to determine whether it has a benign or malignant nature. This enables patients with thyroid cancer to receive adequate therapy in an earlier stage resulting with lower morbidity and mortality, and at the same time precludes unnecessary surgery in patients with benign nodules.[8] The differential diagnosis of thyroid nodules usually require additional diagnostic evaluations.

DW MR imaging can perform quantitative measurement from the motion of water molecules Moving molecules induce a signal loss and this loss affects the ADC value for interested region. The ADC value build up with the diffusion of extracellular space, cellular diffusion and intravascular perfusion. For instance, growing tumors shows increased cellularity and increased amount of diffusion barriers. As a result diffusion capacity is restricted so SI values will rise and ADC values will fall.

In literature several studies have investigated the utility of DWI in distinguishing between benign and malignant nodules and to evaluate the functional activity of the thyroid gland.[13-15]

Tezuka et al. reported that the thyroid gland should be considered to be histologically isotropic organ because similar ADC values can be detected along the different positions within the gland.[13] They also investigated usefulness of DWI in the differentiation of Graves disease, subacute thyroiditis and Hashimoto thyroiditis. They found that ADC values in patients with Graves disease were significantly higher than other two diseases.

ADC measurements can also be used in the differentiation of benign and malignant thyroid nodules and in the literature a few articles were found about this topic even though they gave controversial results. Razek et al. performed first study and showed that the mean ADC values of malignant solitary thyroid nodules (0.73± 0.19 x 10^{-3} mm^2 / s) were significantly lower than those of benign nodules (1.8 ± 0.27 x 10^{-3} mm^2 / s).[16] They determined a cut off ADC value of 0.98 x 10^{-3} mm^2 / s that yielded a 97.5% sensitivity, 91.7% specificity and 98.9% accuracy for the differentiation between benign and malignant nodules. In their study DWI was obtained with b values of 0, 250 and 500 s / mm^2. Erdem G et al. in their recently published study consisting of 52 benign and 9 malignant nodules found that the mean ADC values of malignant thyroid nodules (0.69±0.31 x 10^{-3} mm^2 / s) were significantly lower than those of benign nodules (2.74±0.60 x 10^{-3} mm^2 / s).[12] They used b values of 0 and 1000 s / mm ^{2} to obtain DWI and found similar results for malignant nodules with Razek et al. Another study performed by Bozgeyik Z et al. included 88 benign and 5 malignant thyroid nodules.[17] They used b factors of 100, 200 and 300 s / mm^2 for ADC measurements. The mean ADC values of malignant and benign nodules were 0.96 ± 0.65 x 10^{-3} mm^2 /s and 3.06±0.71 x 10^{-3} mm^2 / s for b-100 factor, 0.56 ± 0.43 x 10^{-3} mm^2 / s and 1.80 ± 0.60 x 10^{-3} mm^2 / s for b-200 factor, and 0.30 ± 0.20 x 10^{-3} mm^2 / s and 1.15 ± 0.43 x 10^{-3} mm^2 / s for b-300 factor, respectively. They concluded that benign thyroid nodules present with higher ADC values than malignant nodules and DWI may be helpful in this differentiation. In our study similar to Erdem G et al. we used b values of 0 and 1000 s / mm ^{2} to obtain ADC values. We found mean ADC values for benign and malignant thyroid nodules 2.11 ± 0.41 x 10^{-3} mm² / s and 1.55 ± 0.31 x 10^{-3} mm² / s, respectively. Similar to the previous three studies, we obtained significantly lower ADC values for malignant thyroid nodules compared to benign ones. Although all of these studies found statistically significant differences between the ADC values of benign and malignant thyroid nodules, the obtained mean ADC values can vary between the studies, probably depending on different b factors used in these studies. Schueller-Weidekamm et al. used DWI with a b factor of 800 s / mm ² in the differentiation of 25 cold thyroid nodules consisting of 20 carcinomas and 5 adenomas.[14] Contrary to the previously mentioned studies, they found thyroid carcinomas had signi ficantly higher mean ADC values (2.73 x 10^{-3} mm² / s) than those of adenomas (1.92 x 10^{-3} mm² / s). An ADC value of 2.25 x 10^{-3} mm² / s or higher was predictive of carcinoma with an accuracy of 88%. In another study performed by Schueller-Weidekamm et al. similarly to the prior one, 35 cold thyroid nodules were investigated by DWI with a b factor of 800 s / mm².[18] Their patient population included 20 thyroid carcinomas, 11 adenomas and 4 cases of Hashimoto thyroiditis. They found median ADC values for carcinoma, adenoma and Hashimoto thyroiditis as 2.73 x 10^{-3} mm² / s, 1.93 x 10^{-3} mm² / s and 3.46 x 10^{-3} mm² / s, respectively. They concluded that although there was a significant difference between the median ADC values of carcinoma and adenoma patients, there was no significant difference avaliable between the carcinoma and Hashimato patients in this study. Again they found a 88% accuracy level for a 2.25 cut off value of ADC in predicting malignancy.

As a general rule malignant tumors have high nucleus/cytoplasma ratio and they show hypercellularity so the malignant thyroid nodules are not exception. These histopathologic characteristics restrict the extracellular matrix and the diffusion space of protons. This results ADC values to be decreased.[15] Therefore ADC values in benign nodules are higher due to the increased mobility of protons as expected. Razek et al. explained ADC value differences not only with differences of cellularity, but also histopathologic features.[16] For instance abundant hyperplastic nuclei and calcified psammoma bodies in papillary carcinoma may be responsible from lower ADC values. However, Schueller-Weidekamm at al. claimed that this explanation could be stated as a general malignant tumor rule not only for thyroid malignancies.[18] They also concluded, as a result of macrofollicular production of thyreoglobulin, diffusion capacity can be unrestricted. Additionally the presence of microcalcifications affect MR signal intensity. On the contrary Wang et al. reported that, malignant head and neck lesions have increased diffusion capacity with resultant high ADC values for thyroid carcinomas.[15] Their explanation for these high ADC values was increased extracellular fluid in the follicular portions of these tumors.

After ROC analysis a cut off value of 1.81 x 10^{-3} mm² /s was determined which yielded a 85.7% sensitivity, 69.7% specificity, and 74.47% accuracy. Overall accuracy is fairly good.

In this study for DWI we used b factor of 0 and 1000 s / mm². In that way, we obtained good quality images with adequate signal-to-noise-ratio. The reason for choosing b value was to reduce the influence of perfusion effects on DWI. Thus our ADC values, in fact, reflected the diffusion capacity in benign and malignant thyroid nodules without being influenced much by perfusion effects.

There are several limitations of our prospectively designed study. First, our patient population was relatively small and therefore ADC values obtained for differentiation between benign and malignant thyroid nodules need to be confirmed in larger cohorts. Secondly, we excluded thyroid nodules with a diameter of less than 1 cm due to low spatial resolution of the DWI technique. But in near future, improvements in technology may enable detection of smaller nodules. Thirdly, overlapping was present between benign and malignant thyroid nodules. Finally, the threshold value for the b factor we used in our study should be tested in further studies.

CONCLUSION

Our results suggested that DWI using quantitative parameters is a promising, reliable technique and may help in differentiating benign thyroid nodules from malignant ones; however, further studies with larger patient pool are needed to confirm these results.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

All authors contributed equally this study.

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