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Original article

Role of Diffusion Weighted MRI, Sonography in Characterization of Thyroid Nodules Guided by TIRADS Classification

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Abtract

The goal of this study is to investigate the potential benefits of diffusion weighted echo planer (DWI-EPI) and ultrasonography in differentiation of benign and malignant thyroid nodules in patients referred for fine needle aspiration cytology and correlate the imaging pattern guided by TIRADS classification with their pathological nature.30 patients were included in this study (20 females and 10 males**),** their ages vary from (24 years to 75 years). All patients were referred from outpatient clinic of Beni-Suef university hospital, starting from 8-2019 to 3-2020. In our study there were 20 patients found with benign nodules and 10 with malignant nodules, apparent diffusion coefficient (ADC) value was calculated for both benign and malignant nodules, there was statistically significant lower ADC value in malignant thyroid nodules (0.7±0.1) compared to benign nodules (2.5±0.9) (P-value<0.001),also there was statistically significant association TIRADS 4 and 5 detected by U.S with malignant thyroid nodules proved by biopsy (P-value<0.001).

1. Introduction:

Thyroid nodule is a discrete lesion in the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma (1). Thyroid nodules are common; their prevalence in the general population is high, the percentages vary depending on the mode of discovery: 2–6 % (palpation), 19–35 % (ultrasound) and 8–65 % (autopsy data). They are discovered either clinically on self-palpation by a patient, or during a physical examination by the clinician or incidentally during a radiologic procedure such as ultrasonography (US) imaging, computed tomography (CT) or magnetic resonance imaging (MRI) of the neck (2 , 3).

Thyroid nodules are being diagnosed incidentally with increasing frequency in the recent years (4 , 5). Though thyroid nodules are common, their clinical significance is mainly related to excluding malignancy (4.0 to 6.5% of all thyroid nodules) , evaluating their functional status and if they cause pressure symptoms (6 , 7 ,8) .

Ultrasound is also recommended for all patients to confirm the presence of nodule, define suspicious sonographic features and assess the presence of additional nodules or lymphadenopathy (9 , 10) .

Diffusion-weighted MR imaging (DWI) is non-invasive and does not involve administration of contrast or radiation exposure (11 , 12) .

It provides image contrast through measurement of the diffusion properties of water within tissues. It is used to differentiate benign and malignant lesions where increased cellularity of malignant lesion restricts water motion in a reduced extracellular space. Structural characteristic of malignant or benign tissue will result in different signals on DWI, which may be quantified by calculating the Apparent Diffusion Coefficient (13) .

A TIRADS scoring system was developed to predict the malignancy risk of the thyroid nodules based on six categories US features by a scoring system, which included a standardized vocabulary and score and a quantified risk assessment (14). .

TI-RADS 1: normal thyroid gland

TI-RADS 2: benign lesions

TI-RADS 3: probably benign lesions TI-RADS 4: suspicious lesions (sub-classified as 4a, 4b, and later 4c 4 with increasing risk of malignancy)

TI-RADS 5: probably malignant lesions (more than 80% risk of malignancy)

TI-RADS 6: biopsy proven malignancy (15) .

2. Patients and Methods :

This study was conducted on 30 patients , with palpable thyroid nodule or neck lump that moves with swallowing, diagnosed by clinical examination or ultrasound, and referred from outpatient clinic of Beni-Suef university hospital, starting from 8-2019 to 3-2020.

Inclusion criteria:

Patients having palpable thyroid nodule that move with swallowing , (either newly discovered or increased size of already diagnosed thyroid nodule .

Exclusion criteria:

Patients with functioning thyroid nodules , to avoid possibility of crisis upon FNA.

-Those who have contraindications for MRI such as pacemaker, metallic implants, and claustrophobia were excluded from the study.

-Fixed nodules .

Clinical assessment:

General and Physical Examination including the Size, location and character of palpable thyroid nodules and size and location of palpable neck nodes.

High resolution US:

All ultrasound examinations were performed on a ultrasound scanner (Toshiba xario 200). The probe frequency was 7–13 MHz . During examination, the patient was in a supine position, with the head slightly backward to fully expose the neck. All nodule once identified were categorized based on their characteristics of size , margin , shape , echogenicity , calcifications (macro , micro , punctate , peripheral calcifications) and vascularity in accordance with the ACR TIRADS lexicon . Points were allocated to each nodule based on the ACR TIRADS ,, TR 1=0 points , TR2 = 2 points , TR3 = 3 ,TR4 = 4-6 points , TR5 = 7 or more points .

MRI protocol

All MR imaging (MRI) examinations were performed on a (field strength 1.5 Tesla on Siemens Aera machine). The head and neck coils were placed over the thyroid surface. Patients were placed in a supine position with their neck, back, shoulders relaxed and instructed to breath smoothly and avoid swallowing. The MRI acquisition parameters were:

T2WI (TR = 2500 ms , TE = 100 ms, thickness = 3 mm, gap = 1 mm, FOV = 240 mm × 240 mm, matrix = 300 × 240) , DWI (TR = 400 ms , TE = 70 ms, thickness = 3 mm, gap = 1 mm, FOV = 240 mm × 240 mm, matrix = 220 × 180). The b values were 300 , 500 & 800 s/mm2.

T2-weighted images were used for detection and evaluation of signal characteristics of nodules.

DWI image analysis was performed to measure the average ADC value of each nodule (b value 300 , 500 , 800 s/mm2). For the ADC value, a region of interest of the same size on different sections was selected for multi-point measurement, and the average value was obtained . T2-weighted, and DW images obtained the same levels of thyroid tissue. We avoided ADC measurement of cystic portions of nodules because it could give a falsely elevated ADC value .

Image analysis

ADC maps were computed for each of the b-values used in the DWI protocol. This was done automatically for the b-factors of 300 s/mm^2, 500 s/mm^2 and 800 s/mm^2. ADC values were extracted from the ADC maps. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS, Chicago, Ill). All ADC data were recorded in Mean ± SD ($\times 10^{-3}$ mm^2/s) form. Mann–Whitney U-test was performed to compare the quantitative ADC value of benign and malignant thyroid nodules. A value of $p < .05$ was considered significant. In addition, receiver operating characteristic (ROC) curve was constructed to determine a cutoff value for differentiating benign and malignant thyroid lesions. Receiver operating characteristic (ROC) curves were constructed and areas under the ROC curve were computed .

Statistical analysis

Analysis of data was performed using SPSS v. 25 (Statistical Package for Social science) for Windows (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) Description of quantitative variables was presented in the form of mean± standard deviation (SD) for parametric data and median (range) for non-parametric data.

Description of qualitative variables was presented in the form of numbers (No.) and percent's (%).

Independent T-test was used to detect the difference between groups regarding their normally distributed scale variables or Mann-Whitney for non-parametric data (ANOVA in case of different TIRADS grades).

Chi-Square test (or Fisher's exact) will be used to detect the difference between cases and controls categorical variables.

ROC curve was used to detect the optimal cut-off of ADC level in prediction of malignancy.

The significance of the results was assessed in the form of P-value that was differentiated into:

Non-significant when P-value > 0.05

Significant when P-value ≤ 0.05

3. Results:

This study was conducted on 30 patients with thyroid nodules, 20 patients found with benign nodules and 10 with malignant nodules based on the results of biopsy.

Table (1): Baseline characteristics of patients with benign and patients with malignant nodules:

Characteristics	Benign nodules group n=20(%)	Malignant nodules group n=10(%)	P-value
Age mean±SD	42.6±18.2	56.8±19	0.063
Sex Females Males	15 (75) 5 (50)	5 (25) 5 (50)	0.171

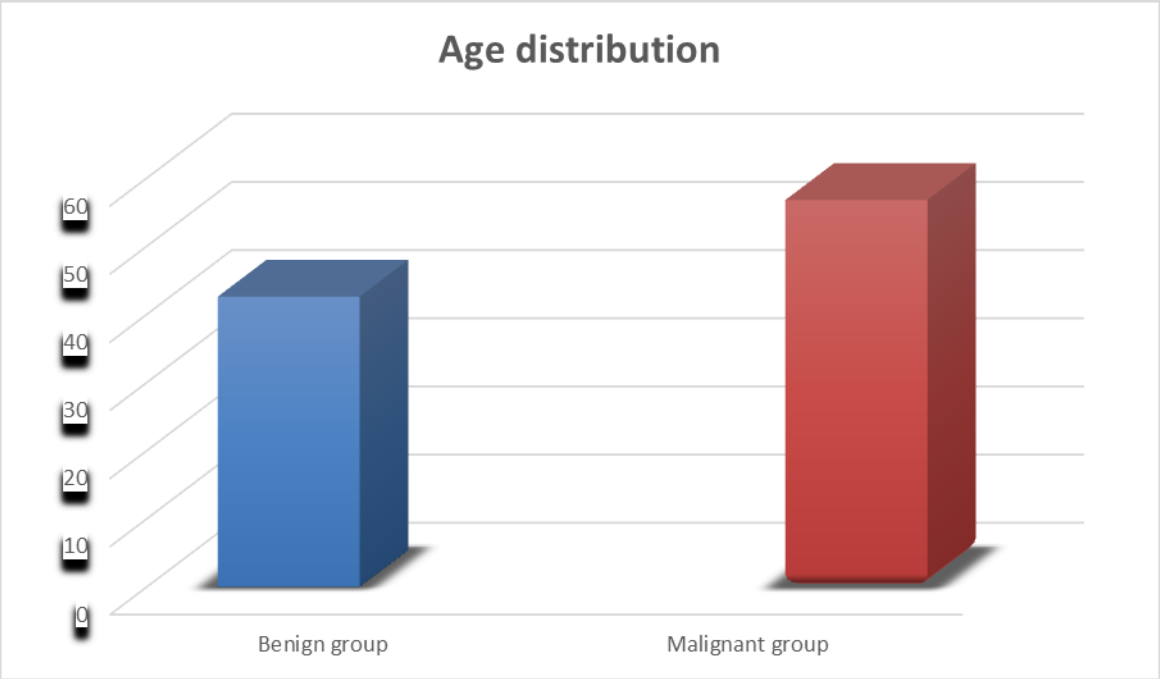


Figure (1)

Table (1) and figure (1) showed that there was no statistically significant difference between patients with benign and malignant nodules regarding their age and sex distribution.

Table (2) Comparison between patients with benign and patients with malignant nodules regarding the ultrasound findings:

Characteristics	Benign nodules group n=20(%)	Malignant nodules group n=10(%)	P-value
Size			
Transverse diameter	2.1±0.8	0.9±0.4	0.001*
Vertical diameter	1.8±.71912	1.4±0.5	0.118
Echogenicity			
Anechoic	6 (30)	0 (0)	
Iso to hypoechoic	6 (30)	0 (0)	
Iso to hyperechoic	2 (10)	0 (0)	<0.001*
Isoechoic	6 (30)	0 (0)	
Hypoechoic	0 (0)	**10 (100)**	
Vascularity			
Avascular	18 (90)	0 (0)	
Peripheral vascularity	2 (10)	0 (0)	<0.001*
Internal vascularity	0 (0)	**10 (100)**	
Calcifications			
No	14 (70)	1 (10)	
Macrocalcification	6 (30)	0 (0)	
Peripheral	0 (0)	**4 (40)**	<0.001*
Punctate	0 (0)	**5 (50)**	
Shape			

Wider than tall Taller than wide	20 (100) 0 (0)	2 (20) **8 (80)**	<0.001*
Margin Regular Irregular	 20 (100) 0 (0)	 2 (20) **8 (80)**	<0.001*
Composition Cystic Complex cystic and Solid Solid	 14 (70) 6 (30) 0 (0)	 0 (0) 0 (0) **10 (100)**	<0.001*
Lymph Node Nil Nonspecific Suspicious (globular ,thick cortex &effaced fatty hilum)	 11 (55) 9 (45) 0 (0)	 2 (20) 0 (0) **8 (80)**	<0.001*
Extra thyroid extension No Yes	 20 (100) 0 (0)	 5 (50) **5 (50)**	0.001*

**P-value is significant*

Table (2) showed that there was statistically significant association of suspicious lymph nodes, hypoechoic echogenicity, vascularized nodules, peripheral & punctate calcifications, taller than wide shape, irregular margins, extra-thyroid extension, and solid composition of the thyroid nodules detected by ultrasound among patients proved to have malignant thyroid nodules by biopsy (P-value≤0.001).

Table (3) showed that there was statistically significant association TIRADS 4 and 5 detected by U.S with malignant thyroid nodules proved by biopsy (P-value<0.001).

TIRADS	Benign nodules group n=20(%)	Malignant nodules group n=10(%)	P-value
TIRADS 2	14 (70)	0 (0)	<0.001*
TIRADS 3	4 (20)	0 (0)	
TIRADS 4	2 (10)	**6 (50)**	
TIRADS 5	0 (0)	**4 (40)**	

**P-value is significant*

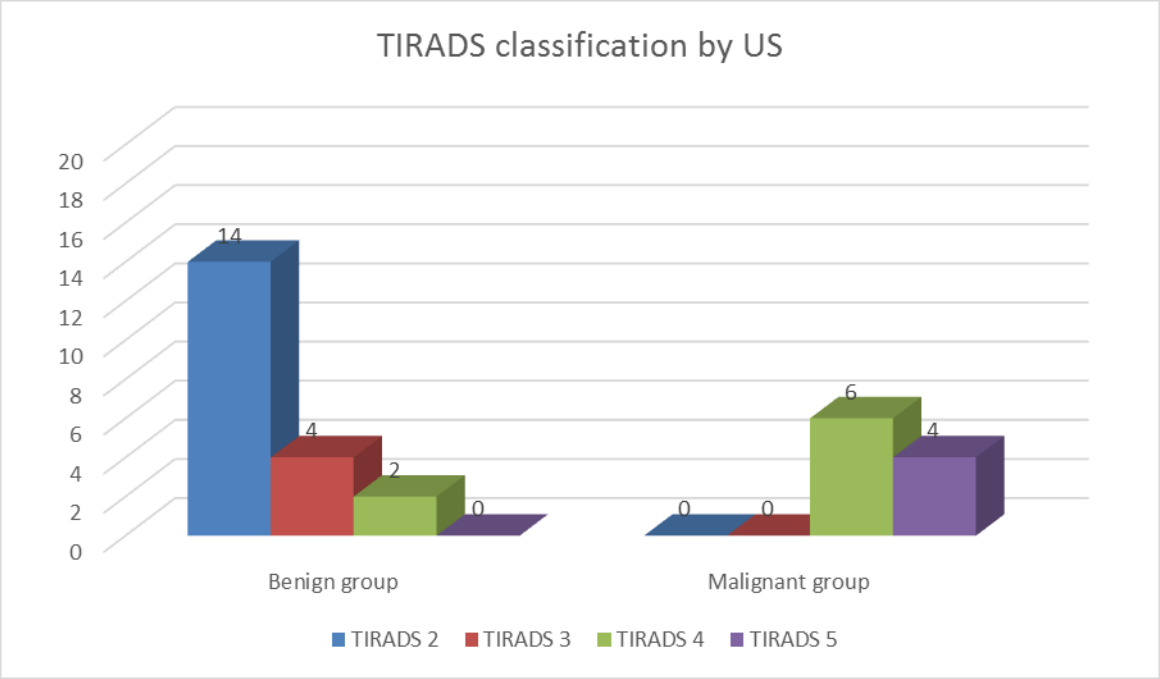


Figure (2)

Table (3) and figure (2) Comparison between patients with benign and patients with malignant nodules regarding the TIRADS classification by ultrasound findings:

Table (4) Comparison between patients with benign and patients with malignant nodules regarding the ADC value

ADC value x 10^{-3} mm	**Benign nodules group n=20(%)**	**Malignant nodules group n=10(%)**	**P-value**
Mean±SD	2.4±0.5	0.7±0.1	<0.001*
Median	2.5	0.7	
Range (min-max)	(1.4-2.8)	(0.5-0.9)	

**P-value is significant*

Table (4) showed that there was statistically significant lower ADC value in malignant thyroid nodules (0.7±0.1) compared to benign nodules (2.5±0.9) (P-value<0.001).

Table (5) sensitivity, specificity, positive predictive value and negative predictive value of ADC in detection of malignancy referenced by histopathological examination:

Items	Values
Cut off	≤0.85
P-value	<0.001*

Area under curve	0.989
Sensitivity (95% CI)	100 (66.4 – 100)
Specificity (95% CI)	95.24 (76.2 - 99.9)
PPV (95% CI)	90 (57.1 - 98.4)
NPV (95% CI)	100 (85-100)

Table (5) showed that there was a significant role of ADC value in prediction of malignant thyroid nodule at a cut off 0.85 or less with 100% sensitivity, 95.24% specificity, 90% PPV and 100 NPV.

Table (6) sensitivity, specificity, positive predictive value and negative predictive value of ultrasound TIRADS classification in detection of malignancy in reference to histopathological examination:

			Biopsy		**Total**
			Benign	**Malignant**	
US	**Benign**	Count	18	0	18
		% within US	100.0%	0.0%	100.0%
		% within biopsy	90.0%	0.0%	60.0%
	Malignant	Count	2	10	12
		% within US	16.7%	83.3%	100.0%
		% within biopsy	10.0%	100.0%	40.0%
Total		Count	20	10	30
		% within US	66.7%	33.3%	100.0%
		% within biopsy	100.0%	100.0%	100.0%

Table (6) showed that the ultrasound can detect malignant thyroid nodules with 100% sensitivity, 90% specificity, 83.3% PPV and 100% NPV.

Table (7) Comparison between sensitivity, specificity, positive predictive value and negative predictive value of ultrasound and ADC value:

Items	**ADC**	**US**
Area under curve	0.989	0.950
Sensitivity (95% CI)	100 (66.4 – 100)	100 (69.2 – 100)
Specificity (95% CI)	95.24 (76.2 - 99.9)	90 (68.3 - 98.8)

PPV (95% CI)	90 (57.1 - 98.4)	83.3 (57.3 - 94.9)
NPV (95% CI)	100 (85-100)	100 (80-100)

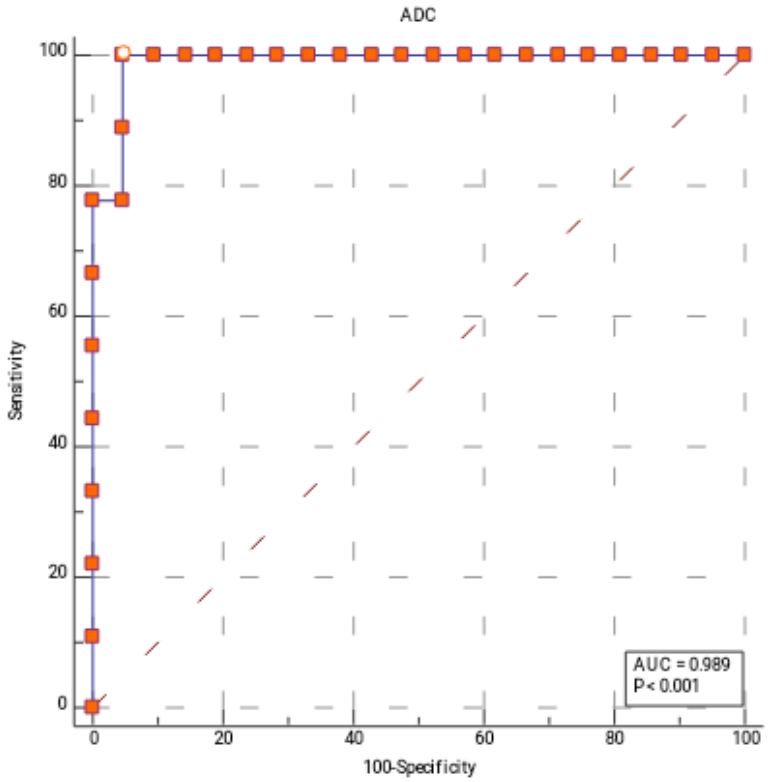
Table (7) showed that both ultrasound and ADC significantly detect malignant thyroid nodules (referenced by biopsy) but the ADC value had higher specificity and positive predictive value.

Table (8) Comparison between different grades of TIRADS classification in malignant group regarding the ADC value:

TIRADS	Number	mean	SD	P-value
TIRADS 4	2	0.72	0.2	0.061
TIRADS 5	6	0.63	0.1	

Table (8) showed that there was no statistically significant difference in different TIRADS grades among the malignant thyroid nodule group.

Figure (3) Receiver operating characteristic curve analysis for detection of the optimal cut off ADC in prediction of malignant thyroid nodules



4. Discussion:

The study was conducted on 30 patients , with palpable thyroid nodule or neck lump that moves with swallowing,(diagnosed by clinical examination or ultrasound) . 20 patients with benign nodules and 10 with malignant nodule based on the results of biopsy.

There were 20 females and 10 males with benign nodules' mean age of 42.6±18.2 years and malignant nodules' mean age of 56±19 years .Nodules were characterized by their : size , shape , margins, echogenicity , calcifications , vascularity , extra-thyroid extension and presence of lymphadenopathy based on the TI-RADS .

Ultrasound features associated with malignancy are micro-calcifications, hypo-echogenicity, irregular margins or absent halo sign, solid aspect, intra-nodular vascularization, and shape (taller than wide) .

Cheng reported that the blood flow characteristics of nodules could be used as an important reference index for differentiating benign and malignant nodules. However, there were some overlaps between benign and malignant nodules on sonograms, and previous studies suggested that the TI-RADS classification is still controversial. (85) .

In our study there Of these nodules, 5 were categorized as TIRADS 2 : 14 , as TIRADS 3 : 4 , as TIRADS 4 : 8 and 4 as TIRADS 5.

There was significant association with TIRADS 4 and 5 detected by U.S with malignant thyroid nodules . However two nodules suggested to be malignant and classified as TIRADS 4 by ultrasound but there pathological data revealed benign nature

Other studies as **Weidan Kong** showed that Malignant nodules have blurred boundaries, solid hypoechoic interiors, gravel-like calcification, and mixed internal blood flow.

The sensitivity of ultrasound diagnosis of nodules was high (90.1%), but the specificity was not (80.4%). (16,17).

In our study there was strong association between hypo-echoic nodules and malignancy but benign nodules exhibit either anechoic , iso to hyper or iso to hypo-echogenicity .regarding the composition malignant nodules were almost solid and benign nodules were either cystic or complex cystic and solid . Malignant nodules showed mainly peripheral or punctate calcifications and few of benign nodules had macro-calcifications .There was close association between internal vascularity and malignant nodules and most of benign nodules were avascular and few of them showed just peripheral vascularity .

The ultrasound can detect malignant thyroid nodule with 100% sensitivity , 83.3 % specificity , 90 % PPV and 100 % NPV .

Ota reported that an enhanced posterior echo of nodules is an important differentiating sign of lymphoma compared to other malignant thyroid tumors; benign nodules have clear boundaries, low-signal and isoechoic interiors, and may be accompanied by coarse calcium. Most of the

lesions had complete capsules, with rare blood flow signals in the nodules (18) .

DWI has emerged as a noninvasive and complimentary tool in the assessment of thyroid nodules .. The main problem with obtaining DWI in head and neck tissues is the motion artifact, caused by nearby moving organs. Breathing, swallowing, coughing, and jaw movements can greatly affect the quality of the images . To minimize the degree of motion , we give simple instruction/education of the patient to hold still while the scanner is working . Pre-scan training and practice with breath holding may be helpful.

The patient should be made as comfortable in the scanner as possible, including back, leg, or head supports. Stabilization measures including the use foam pads . Uncooperative patients or those with high anxiety or pain were excluded . **Neck coil** also used to minimize unwanted signals from moving tissues located farther away .

There was statistically significant lower ADC value in malignant thyroid nodules (0.7±0.1 × 10−3 mm2/s) compared to benign nodules (2.4±0.5 × 10−3 mm2/s) . We estimated a cut off value of 0.85 × 10−3 mm2/s or less in prediction of malignant nodules with 100% sensitivity, 95.24% specificity, 90% PPV and 100 NPV.

A number of studies have evaluated the role of DWI for assessment of thyroid nodules. **Erdem** found significantly increased ADC value in benign and significantly decreased ADC value in malignant thyroid nodules compared to the normal thyroid parenchyma The mean apparent diffusion coefficient (ADC) values of thyroid nodules were (1605-3899 x 10(-6)mm(2)/s) in the benign group and 695.2 +/- 312.5 x 10(-6)mm(2)/s (165-1330 x 10(-6)mm(2)/s) in the malignant group . (18) .

Study by Razek et al. found that the mean ADC value of malignant solitary thyroid nodules was 0.73 +/- 0.19 x 10(-3) mm(2)/s and of benign nodules was 1.8 +/- 0.27 x 10(-3) mm(2)/s. The mean ADC values of malignant nodules were significantly lower than those of benign ones (P = .0001). There were no significant differences between the mean ADC values of various malignant thyroid nodules, (19) .

Also, in the study made by El- Hariri et al. the mean ADC of the benign thyroid nodules were 1.85 ±0.24 X l0–3 mm2 /s while the mean ADC of the malignant thyroid nodules was 0.89 ±0.27 X 10–3 mm 2 /s (20) .

Aydin et al. also concluded that malignant nodules had significantly lower ADC values than the benign ones also, mean ADC values among the subtypes of malignant nodules had no significant differences. This was in agreement with our results (21).

The b-factor in the DWI was an important factor for image quality. We obtained diffusion-weighted MR images with different b factors simultaneously to avoid mis-registration in computing the different ADC values In this study, we applied an SE EPI diffusion imaging with b-factors of 300, 500 and 800 s/mm2 . EPI

is the fastest acquisition method and it only requires 30 ms ~ 100 ms to collect one image which helps in reducing most physiological movement artifacts .

Other studies used different b values , for example :

Aydin et al. calculated the ADC values for both malignant and benign nodules as an average results of b factor 200 and 400 s/mm2 (21) .

Erdem et al. used b values of 0 and 1000 s/mm2 (22) .

Mutlu et al. in their study used b values of 0, 50, 400 and 1000 s/mm2 (23) .

The study was subject to several limitations, which should be considered when interpreting the results :

First, the number of malignant nodules was low and the results of this study might be confirmed in those with higher number of malignant nodules.

Second, nodules measuring below 7 mm could not be evaluated with DWI.

Third , we did not evaluate the whole lesion ADC value and only evaluated ADC value of the lesion excluding cystic and necrotic components .

Fourth. there was a lack of histological correlation in some cases which hindered the ability to provide confirmatory diagnosis of suspicious nodules

Fifth , the presence of motion artifact made the interpretation difficult in some individuals.

Finally the advent of COVID 19 resulted in drop in patients number and follow up of those who required histopathological correlation .

List of Abbreviations

ADC : Apparent diffusion coefficient,

AUC : Area under the ROC curve ,

FOV : Field of view ,

ROC : Receiver operating characteristic ,

ROI : Region of interest,

TE : Echo time,

TR : Repetition time .

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