THE ROLE OF DIFFUSION WEIGHTED MRI STUDY AND ITS QUANTITATIVE PARAMETER, APPARENT DIFFUSION COEFFICIENT VALUE, TO DIFFERENTIATE MALIGNANT FROM BENIGN THYROID NODULES

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ABSTRACT

Thyroid nodule evaluation is usually done using ultrasound examination and a fine needle aspiration cytology/biopsy. The aim of this study was to evaluate the role of diffusion weighted imaging to differentiate benign from malignant thyroid nodules. Fifty five patients, 3 males (5.5%) and 52 females (49.5%) (17–66 years, mean age 44.4 years) with thyroid nodules were included in the study. Routine MRI of neck and diffusion-weighted MR imaging was performed using b-values 1000. Apparent diffusion coefficient (ADC) values were done for every case. Histopathological results of the thyroidectomy samples were obtained. Comparison of apparent diffusion coefficient values of thyroid nodules with the histopathology was done.The pathology results showed that there were 44 (80%) and 11 (20%) benign and malignant thyroid nodules respectively. The mean maximum diameter of benign and malignant thyroid nodules were 3.5 ±1.3 cm and 2.7± 0.9cm respectively, The mean ADC for being and malignant nodules were 2.10 ±0.49 x10^{-3} and 1.10 ±0.15x 10^{-3} respectively. ADC values for benign and malignant thyroid nodules which were significant ($p< 0.001$).

Keywords: *thyroid gland, thyroid nodules, diffusion weighted imaging, ADC, b-value*

INTRODUCTION

The thyroid gland lies in front of lower part of the neck seen as is a bilobed structure connected by an isthmus and is draped anteriorly around the central airway structures (1). The Thyroid gland develops during the 24th gestational day considered to be the first endocrine gland to develop in the body it originates embryologically from 1st & 2nd pharyngeal pouches (2).

Thyroid gland nodules are considered as the most common thyroid gland pathology that reaches 4%–7% of population. Thyroid nodules prevalence may vary according to the sex, age, and population (3). The national cancer institute, SEER statistics, (Surveillance, Epidemiology, and End Results Program) estimates that the number of new cases of thyroid cancer was 12.9 per 100,000 men and women per year. The number of deaths was 0.5 per 100,000 men and women per year.

Ultrasound is the most important diagnostic imaging modality for characterizing of thyroid gland lesions, it is non-invasive, cheep, non-radiating toll, however there are still no reliable specific criteria are used for differentiating malignant from benign nodules (4).

Thyroid scintigraphy is another noninvasive tool which is used to assess the functional status of thyroid nodule dividing them to cold nodules or hot nodules. The cold nodules as suspicious warning further evaluation, however a large proportion of cold nodules are benign and some functioning nodules (hot nodules) found on scintigraphy proved to be malignant (5).

Ultrasound guided FNAC is a common used tool for diagnosis of thyroid nodules yet it need a well-trained operator and it is incapable of differnating follicular adenoma from follicular carcinoma, And so, there is a challenge to use a reliable noninvasive tool to differentiate benign from malignant nodules.

Diffusion weighted imaging, an emerged MRI technique, uses the principle of random "Brownian" motion of molecules to assess the water diffusion in tissues which is affected by several factors specially the cellularity, extracellular space and integrity of cell membranes (6)

Apparent diffusion coefficient (ADC) is a tool used for quantitative analysis of diffusion restriction. (7).

The malignant thyroid nodules are expected to have more cellular components, larger nuclei denser stroma, these factors will lead to diffusion restriction and so, decrease of ADC values if they compared to benign thyroid nodules (8).

MATERIAL AND METHODS

Patients

The study was done at Fayoum university hospital from Outpatients with solitary or dominant thyroid nodules candidate for surgical thyroidectomy the study was approved by the Faculty of Medicine, Fayoum University Research Ethical Committee. The study group consists of 55 cases 55 nodules. The patient age ranged from 17 to 66 years with mean age of 44.4±11.4 years old, 52 cases were females representing (49.5%) and 3 cases were males representing (5.5%).

MRI

All patients had an MRI study with routine axial T 1(TR 520,TE 14) and T 2 (TR 4000, TE 100) weighted images and in addition a protocol of Diffusion weighted images was applied with acquisition parameters were: TR 3000 msec, TE 60 msec, slice thickness 5 mm, slice gap -1, scan time 3.5min, fat suppression was added. B- factor =1000, it was done in three orthogonal directions and ADC map was generated.

Image post processing

Using the post processing software, ADC maps were automatically generated for each of the b factors according to the following equation ADC= log (SI1/SI2)/(b2-b1), where SI1 and SI2 are the signal intensities of DWIs obtained with different B values ADC values will be extracted from ADC maps. Circular ROIs (regions of interests) will be carefully placed on the lesions (areas of necrosis, hemorrhage, calcium and cyst formation were excluded). ROIs were placed on one ADC map and. To minimize noise, three measurements will be taken for each lesion and the mean ADC value was recorded. Average of three measurements for each nodules is used, Pathological studies with post-operative histopathological were for every case.

Statistical Analysis

- Data was collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 under windows 7.
- Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data, and inferential statistic test:

- **<u>For quantitative parametric data</u>:**
  - In-depended **student t-Test** used to compare measures of two independent groups of quantitative data
  - One way **ANOVA** test in comparing more than two independent groups of quantitative data.

- **Sensitivity and specificity test for testing a new test with ROC curve "**Receiver Operating Characteristic".

- The level $P \leq 0.05$ was considered the cut-off value for significance.

RESULTS

The study was conducted on 55 cases with 55 solitary or dominant thyroid gland nodules, the cases has an mean age of 44.4±11.5 years old ranging from 17 to 66 years These 55 cases included 3 males representing (5.5%) and 52 females representing (49.5%). There were 29 nodules are seen at right thyroid lobe (52.7%), 20 nodules seen at left thyroid lobe (36.4%) and 6 nodules seen at the isthmus (10.9%), The pathology reports done after surgical operations showed that we have 44 benign thyroid nodules representing about 80% of total nodules and we have 11 malignant thyroid nodules representing 20% of the total nodules. Among the benign group we have 24 adenomatous nodules representing 43.6% and 20 follicular adenoma representing 36.4%, and among the malignant group we also have 6 nodules proved to be papillary carcinoma representing 10.9% and the other 5 nodules proved to be follicular carcinoma representing 9.1%.

The mean age of patients of malignant thyroid nodules were 42.5 ±11.3 years ranging between 24 and 56 years with a median age of about 46 years. The mean age of the patients with benign thyroid nodules was 44.9 ± 11.6 years ranging between 17 and 66 years with a median age of 49 years.

Table 1. *Descriptive parameters of benign and malignant thyroid nodules regarding age and size of the nodules*

Variables	Malignant (n=11)		Benign (n=44)	
	Mean (min –max)	SD	Mean (min –max)	SD
Age (years)	42.5 (24-56)	11.3	44.9 (17-66)	11.6
Nodules size (cm)	2.7 (2- 4)	0.9	3.5 (2-7)	1.3

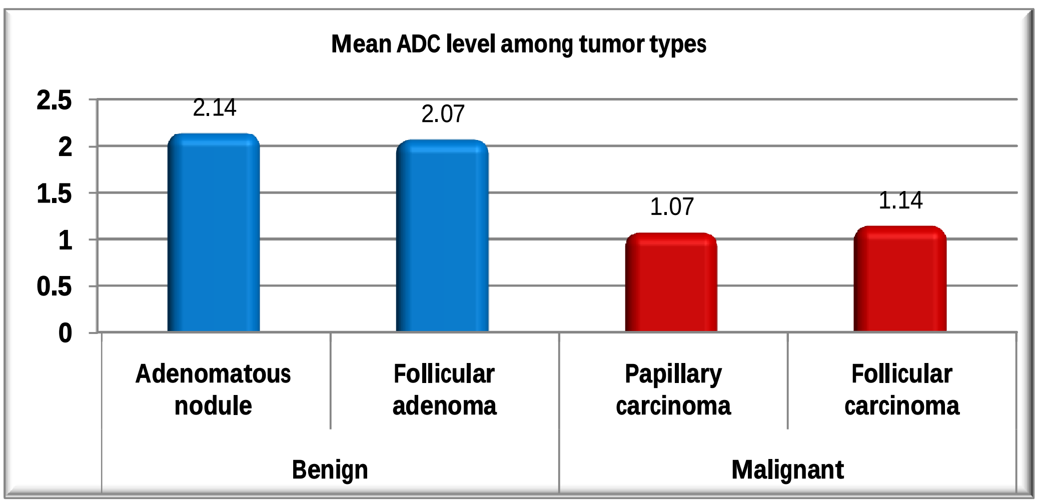

Figure 1*. Bar graph showing mean ADC value between different subtypes of benign and malignant thyroid nodules*

The mean maximum diameter of malignant thyroid nodules was 2.7± 0.9cm The size of malignant nodules ranges from 2: 4 cm, with median maximum diameter is about 2.5cm.The mean maximum diameter for benign nodules was 3.5 ±1.3cm.The size of benign nodules ranges from 2 : 7 cm with median maximum diameter is about 3.5cm.

Table 2. *Subtypes of benign and malignant nodules showing no statistical significant them as regarding ADC values (NS refers to not significant)*

Variables (n=55)	**ADC level**		**p-value**	**Sig.**
	Mean	**SD**		
Type of malignant tumor				
Papillary carcinoma	1.07	0.40	0.7	NS
Follicular carcinoma	1.14	0.59		
Type of benign tumor				
Adenomatous nodule	2.14	0.15	0.5	NS
Follicular adenoma	2.07	0.15		

The mean ADC for that of being nodules was 2.10 ±0.49 x10-3. The mean ADC for that of malignant nodule the mean was 1.10 ±0.15x 10-3 with significant statistical difference between them <0.001**,** the mean ADC value for adenomatous nodule was 2.14 ±0.40 $x10^{-3}$, for follicular carcinoma 2.07±0.59 $x10^{-3}$, for papillary carcinoma 1.07±1.15 $x10^{-3}$ and for follicular carcinoma 1.12 ±0.15 $x10^{-3}$. There is no significant difference between subtypes of benign and malignant nodules P value is 0.5 and 0.7 respectively.

We also used the ROC curve to determine a cut off value which shows that at a cut of value 1.17 $x10^{-3}$ we have 97.7% sensitivity and 81.8% specificity with 97.1% accuracy.

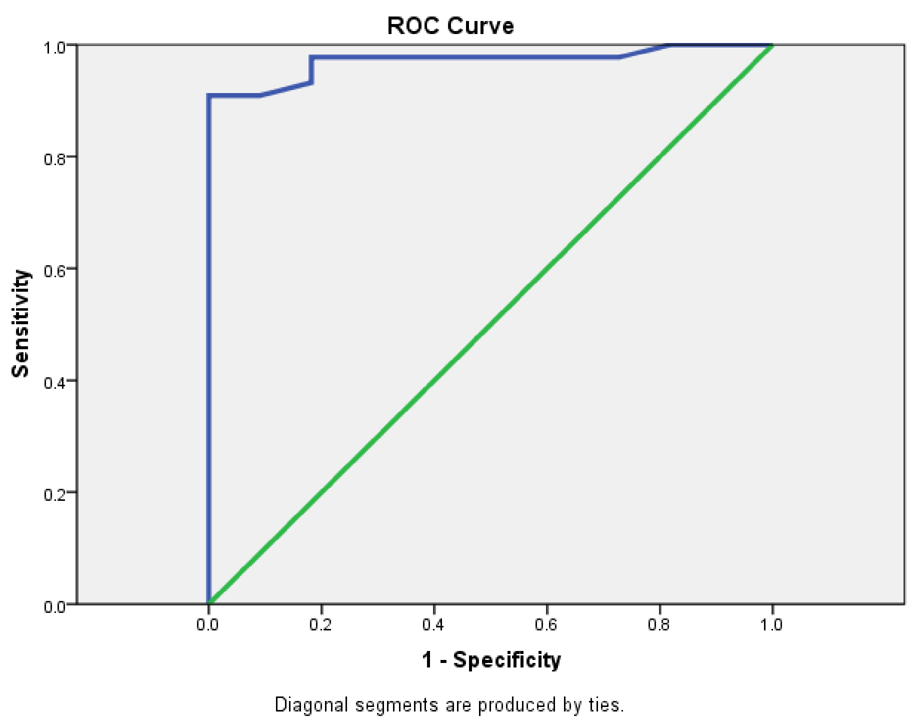

Figure 2*. ROC curve*

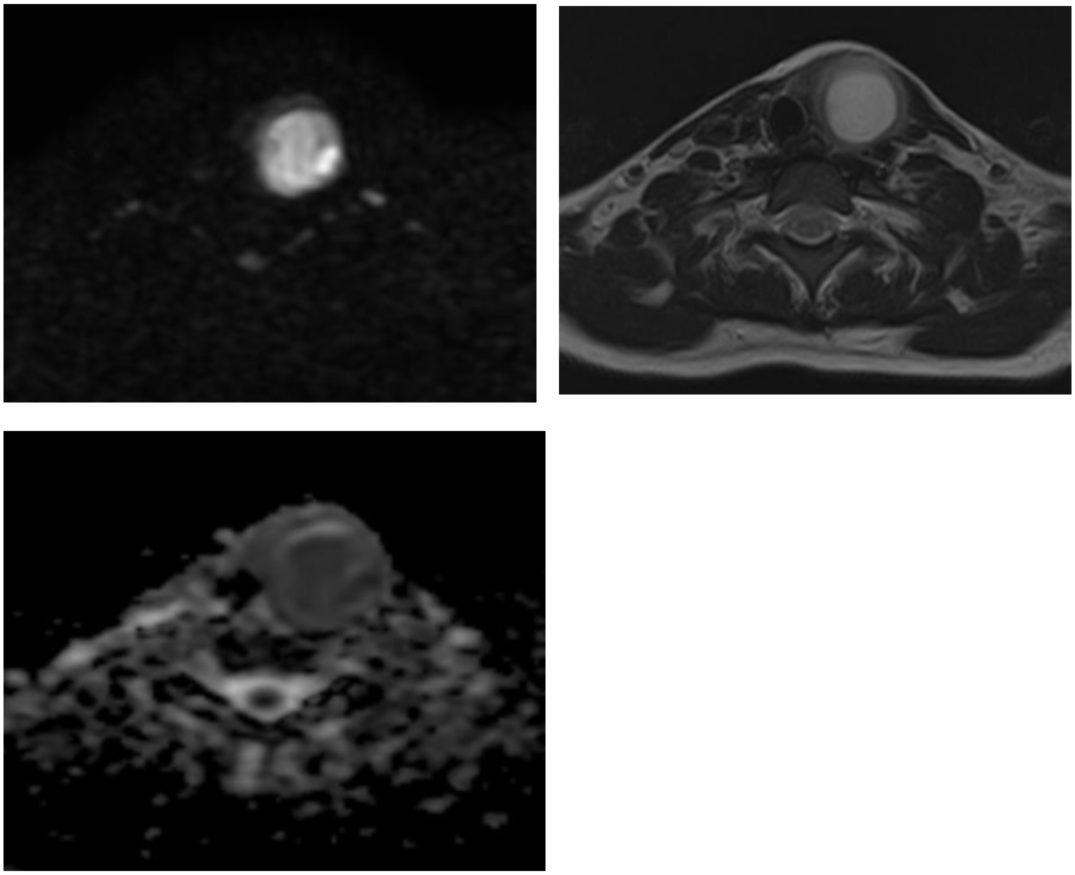

Figure 3. *Malignant left thyroid nodule, A axial DWI and B axial T2 and axial ADC map showing a left thyroid nodule of rounded shape that elicit high T2 signal with high DWI signal denoting restricted,AT ADC map, ADV value was 0.9x10^{-3}*

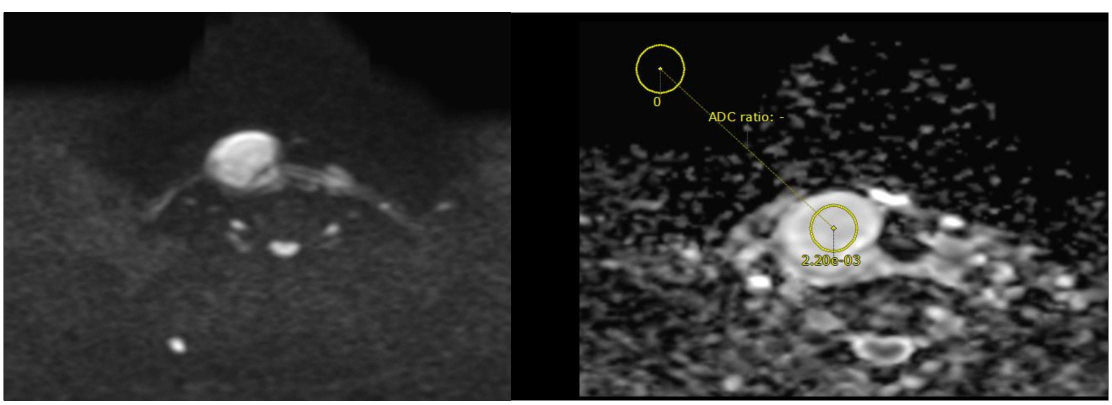

Figure 4. *Benign right thyroid nodule, A axial DWI, B: axial ADC map DWI showing right thyroid nodule of rounded to oval shape with high DWI signal, at ADC map, the ADC value was measures about 2.2x10^{-3}.*

DISSCUSION

Thyroid nodules, the most common pathology involving the thyroid gland, Malignancy occurs in 5%–7% of all thyroid nodules (9,10). In 2014, approximately 62,980 new cases of thyroid carcinoma will be diagnosed and approximately 1890 cancer deaths will occur from the disease in the United States (11). This necessitate search for a precise, noninvasive tool to differentiate benign form malignant thyroid nodules and predict preoperatively nature of the nodules helping in planning a preoperative map for the management of thyroid cases specially the malignant cases. We found some studies evaluating the role of functional MRI as a new non-invasive tool for predicting the nature of the nodule depending upon the diffusion weighted imaging.these studies showed that DWI has the potential to differentiate benign from malignant thyroid nodules with high sensitivity and specificity.

The idea of these studies are to measures the diffusion quantitatively, through the ADC values, considering that malignant nodules will show diffusion restriction and that benign nodules will shows relative free diffusion due to the expected more cellularity of the malignant nodules comparing them with benign nodules, the use of statistics tool could determine the sensitivity and specificity at a certain cutoff value.

At our study we detected 55 solitary or dominant thyroid nodules (44 benign and 11, malignant representing 80% & 20% respectively) a mean ADC of being nodules was 2.10 ±0.49 $x10^{-3}$ and for malignant nodules was 1.10 ±0.15x 10^{-3} with Significant statistical difference between them <0.001 we detected a cut off value 1.17 with 97.7% sensitivity and 81.8% specificity with 97.1% accuracy.

El Aziz et al. (2015) (12) examined 38 benign nodules and 23 malignant nodules with three b values, at b value 300, the mean ADC value of 2.33 ± $0.47x10^{-3}$ for benign nodules and 1.13 ± $0.60 \cdot 10^{-3}$ for malignant nodules with statistical significance ($p<0.001$) between them and 100% specificity and 76% sensitivity.

Nakahira et al. (2012) (13) detected a mean ADC value for benign nodules about 1.93 ± 0.37 $x10^{-3}$ and for malignant nodules about 1.20 ± 0.25 $x10^{-3}$. With a cut value of 1.60 × 10^{-3} has 83 %sensitivity and 94% specificity.

Wu et al. (2013) (14) examined 28 benign nodules and 14 malignant nodules with B- value 1000 showing mean ADC value of benign nodules was 2.37 ± 0.47 $x10^{-3}$ and that for malignant nodules was 1.49 ± 0.60 × $x10^{-3}$ and detected statistical significance ($p<0.001$) between them with a cut off value of, 2.17 has sensitivity of 77% and specificity 0f 100%.

El shafey et al.(2014) (15) examined 28 benign nodules and 13 malignant nodules using b-value 1000 showing a mean ADC value for being nodules about 1.78 ± 0.21 $x10^{-3}$and for malignant nodules 0.59 ± 0.24 $x10^{-3}$,they shows statistical difference between them with 96% sensitivity and 92 specificity.

However in Schueller et al. (2009) (16) study, reported an opposite result to us, they detected ADC values to be higher in malignant thyroid nodules rather than those in benign nodules, with cutoff value 2.25x $x10^{-3}$, the mean ADC value for malignant nodules is 2.73±0.65 x $x10^{-3}$and the mean ADC value for benign nodules is 1.93±0.25 $x10^{-3}$, in this study patient with thyroid nodules who had a radioisotope and cold nodules are chosen for MRI diffusion study. The study includes fewer number of benign nodules and larger number of malignant nodules.

The difference in cut off value, sensitivity and specificity between different study is likely justified by the many factors as few number of patients included in most of studies specially the malignant cases, also the difference in the b value used between different studies, We used b- value 1000, this is agree with studies of Mutlu et al. (2012) (17) & Erdem et al. (2010) (3) & Nakahira et al. (2012) (13), other studies like El Aziz et al. (2015) (12) and Wu et al. (2013) (14) used b-value 300, 500 and 800. Higher B value will better appearance of the diffusion difference between tissues,yet it will affect the image quality as it is associated with low signal noise ratio,this is an explanation for some other studies that used lower b-value to increased signal noise ratio.

We found that no significant statistical difference Comparing between follicular adenoma and adenomatous nodule, p value less than 0.5 (non-significant) and also no significant statistical difference Comparing between follicular carcinoma and papillary carcinoma revealed no significant difference p value less 0.7 (non-significant).

Nakahira et al. (2012) (13) reported that there were no significant difference between the ADC values of adenomatous goiter and follicular adenoma (P=.7 or between those of papillary thyroid carcinoma and follicular thyroid carcinoma (P=.5) Elshafey et al. (2014)(15) detected also that no statistically significant differences found in ADC values among the different benign lesions or among the different malignant.

Limitations to study

This study has some diagnostic limitations. Frist the small number of malignant nodules, and all subtypes if malignant pathological are note represented, 2nd the exclusion of small lesions (less than 1 cm) may lead to miss some malignant cases, also the use exclusion of cystic component may also lead to miss cystic papillary carcinoma. 3rd For the ROI placement, despite our efforts for precise placement and three repeated measurements to minimize any possible errors, there were unavoidable errors including the partial volume effect for the small and irregular lesions,

CONCLUSIONS

The use of diffusion weighted image and ADC can play an important role as an noninvasive technique, DWI has a high sensitivity and specificity, and maybe a reliable, non-invasive imaging modality for the detection of thyroid nodules nature. However large-scale trials, including larger number of malignant cases, are necessary to evaluate clinical importance of DWI and to establish standard b values and cut-off values for DWI-based diagnosis.

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