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ROLE OF DIFFUSION-WEIGHTED MR IMAGING OF THYROID NODULES

By

Shawky M. Deabes, Mohammad H. El-Shafey, Hytham M. Nafady*, and Hytham A. Fath El- Bab

Department of General Surgery and Department of Radio-diagnosis*, Faculty of Medicine, Al-Azhar University

Corresponding author: Hytham A. Fath El-Bab,

Mobile: 0122437861, **E-mail:** drhaythm48@gmail.com

ABSTRACT

Background: Thyroid nodules are the most common disorder of thyroid gland. In Egypt, nodular goiter occurs in 4%-7% of the population. New radiological imaging techniques might be promising for the differential diagnosis of thyroid nodularity's.

Objective: to determine the diagnostic role of diffusion weighted imaging (DWI) in the differentiation of malignant and benign thyroid nodules by using histopathological study as the reference standard.

Patients and Methods: 35 patients were included in this study (28 females and 7 males), their ages vary from (12 years to 75 years) with mean age of 48.65 (±14.72). All patients were referred to the surgical department, El Houssin University Hospital in the time period from July 2018 to August 2019 with thyroid gland enlargement. Results: In our study, there were 7(20.6%) males and 28 (80%) females in the patients group. Percentage of benign thyroid nodule was 52.9%. Percentage of malignant thyroid nodules was 47.1%. apparent diffusion coefficient (ADC) value was calculated for both benign and malignant nodules, the range of ADC values for benign thyroid nodules were (0.03 to 3.5) of mean (1.86 ± 0.82) and (0.5 to 1.5) of mean (1.04 ± 0.2), p value was significant with a cut off value 1.2 with 93% sensitivity and 83% specificity.

Conclusion: DWI provides very useful and promising results on the nature of a thyroid nodule. Even these results may have a role in the selection of nodules that were going to undergo fine-needle aspiration cytology (FNAC). Although these results were promising, further investigations are needed with larger patient groups.

Key words: Diffusion-Weighted MRI, thyroid nodules.

INTRODUCTION

Nodular thyroid is commonly detected on palpation in 4%–7% of the population *(Zamora and Cassaro, 2018)* on sonographic examination in 10%– 40%, and by pathologic examination at autopsy in 50%. In contrast, compared with the high prevalence of nodular thyroid disease, thyroid cancer is rare. The challenge of imaging thyroid nodules is to reassure most patients who have benign disease and to diagnose the minority of patients who will prove to have a malignancy *(Ly et al., 2016).*

Ultrasonography has been used in the assessment of the thyroid nodules as a primary imaging technique *(Floridi et al., 2019).* Currently, there is no single sonographic criterion that can reliably distinguish benign from malignant thyroid nodules *(Xie et al., 2016)*. The results of predicting thyroid cancer with color

Doppler sonography are controversial, with some reporting that Doppler sonography is helpful and others reporting that it did not improve diagnostic accuracy *(Aslan et al., 2018)*. The hazards of radiation exposure are unavoidable in nuclear scintigraphy, and not all functioning nodules on scintigraphy are benign. The risk of cancer in a cold nodule is 4 times more common than in a hot nodule. Fine-needle aspiration biopsy (FNAB) with cytologic evaluation is commonly used, but it is inconclusive in 15%–20% of patients, in addition to the possible, but less likely, associated hemorrhage *(Popoveniuc Jonklaas, 2012)*. The incidence of cancer in patients with thyroid nodules selected for FNAB is approximately 9.2%–13%.5 FNAB is considered an effective method for differentiating between benign and malignant thy- roid nodules *(Hoang, 2010)*.

Routine T1- and T2-weighted MR imaging has a limited role in the evaluation of thyroid nodules. It cannot distinguish benign from malignant nodules or assess the functional status of thyroid nodules *(Wang et al., 2018)*. 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.

The present study aimed to determine the diagnostic role of DWI in the differentiation of malignant and benign thyroid nodules by using histopathological study as the reference standard.

PATIENTS AND METHODS

This retrospective study was conducted on 35 patients (28 females and 7 males), their ages varied between 12 years and 75 years, with a mean age of 48.65. All patients were referred to the Surgical Department, Al-Hussein University Hospital during the time period from July 2018 to August 2019. The study included patients with thyroid nodules, normal thyroid hormonal and bleeding profiles who underwent MR neck for evaluation of thyroid nodule.

Patients who did not have MRI exam before pathology, MRI exam with degraded quality, or patients who did not have pathology after MRI were excluded from the study.

All patients were subjected to MRI using Philips Achieva 1.5T, ultrasound-guided PATHOLOGY and Cytological examination and underwent total thyroidectomy. Histopathological analysis was studied.

MRI was performed using a 1.5-T system (Achieva 1.5-T Pulsar, Philips Healthcare). The basic sequences were obtained in axial planes. The basic MRI protocol consisted of the following sequences; T1-weighted turbo spin-echo imaging (TR/TE: 570/13 & 3-4mm section thickness with a 3-4mm intersection gap), T1- weighted FFE imaging (TR/TE: 300/406 & 3-5mm section thickness with a 3-5mm intersection gap),T2-weighted turbo spin-echo imaging (TR/TE: 6250/105 & 3-4mm section thickness with a 3-4mm intersection gap), diffusion-weighted single-shot turbo spin-echo echo-planar imaging (TR/TE: 2500/70, b factors: 0-

400-800s/mm2 & 3-4mm section thickness with a 3-4mm intersection gap). ADC maps were reconstructed.

MR images were reviewed on DICOM viewer and signal intensities of thyroid nodules and paraspinal muscle on T1-weighted imaging, T2-weighted imaging, ADC were measured pixel by pixel. For each measurement, mean signal intensities were obtained by placing a circular ROI cursor. For thyroid nodules, signal intensities were measured with a circular ROI drawn to encompass the entire nodule at the largest cross-section area as much as possible, carefully excluding artifacts or cystic portions of thyroid nodules. The signal intensity ratio (SIR) was calculated for each sequence as a ratio of signal intensity of the thyroid nodule to that of the Para spinal muscle.

Statistical Analysis:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using mean, standard deviation, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of ADC and SIR for detection of malignancy. P-values less than 0.05 were considered as statistically significant.

RESULTS

¬Patients were grouped according to final pathological diagnosis into 2 groups the benign group and the malignant group, the former included 19 patients, the latter included 16 patients **(Table 1)**.

Table (1): Distribution according to sex of patients and percentage of benign and malignant lesions

Parameters	Count	Percentage
Sex distribution		
Male	**7**	**20%**
Female	**28**	**80%**
Pathology		
Benign	**19**	**54.3%**
Malignant	**16**	**45.7%**

The distribution of benign and malignant lesions in males were 6 and 2 lesions respectively, the distribution of benign and malignant lesions in females were 13 and 14 lesions respectively, P value was insignificant (0.405) **(Table 2)**.

Table (2):Demonstrates the distribution of pathology according to sex

Pathology		Benign		Malignant		P value
		Count	%	Count	%	
Sex	M	6	31.6%	2	12.5%	> 0.05
	F	13	68.4%	14	87.5%	

The diagnosis of different lesions by cytology was: 2 cases of medullary thyroid cancer, 10 cases of papillary cancer, 2 cases of follicular carcinoma and 2 cases of thyroiditis with atypical lymphocytic infiltrates. All of the above lesions were malignant. The benign lesions were classified 12 colloid nodular goiters, and 7 benign follicular neoplasm **(Table 3)**.

Table (3):Different cytological results among the patients

Cytology	Number of patients
Medullary thyroid cancer	2
Papillary thyroid cancer	10
Thyroiditis with atypical lymphocytic infiltration	2
Colloid nodular goiter	12
Benign Follicular neoplasm	7
Follicular carcinoma	2

The size of benign nodules were ranged from 0.1 to 25 cm2 with mean of 5.16 ± 5.9 and the size of malignant nodules were ranged from 0.2 to 8 cm2 with mean of 2.36± 2.07, the size of thyroid of thyroid nodules were insignificantly related to the pathology **(Table 4)**.

Table (4): Range of size of thyroid nodules involved in the study

Pathology			P value
Benign	Mean	5.16	> 0.05
	SD	5.92	
	Minimum	0.1	
	Maximum	25	
Malignant	Mean	2.36	
	SD	2.07	
	Minimum	0.2	
	Maximum	8	

Signal intensity ratio of T1 sequence of benign and malignant nodules were calculated, it ranged from (0.01 to 2.75) in benign lesions of mean (1.03 ± 0.51) and (1 to 1.6) of mean (1.22 ± 0.2) in malignant nodules, area under curve was 0.78, p value was insignificant (0.3) **(Table 5)**.

Table (5): Range of SIR T1 in differentiation between benign and malignant thyroid nodules

SIR1			P value
Benign	Mean	1.03	> 0.05
	SD	0.51	
	Minimum	0.01	
	Maximum	2.75	
Malignant	Mean	1.22	
	SD	0.2	
	Minimum	1	
	Maximum	1.6	
SIR T2			P value
Benign	Mean	3.7	> 0.05
	SD	1.1008	
	Minimum	1.5	
	Maximum	6.6	
Malignant	Mean	3.2	
	SD	0.46	
	Minimum	1.7	
	Maximum	4.2	

Area Under the Curve	P value	95% Confidence Interval	
		Lower bound	Upper bound
0.415	> 0.05	0.210	0.620

ADC			P value
Benign	Mean	1.86	<0.0001
	SD	0.82	
	Minimum	0.03	
	Maximum	3.5	
Malignant	Mean	1.04	
	SD	0.2	
	Minimum	0.5	
	Maximum	1.5	

Signal intensity ratio of T2 sequence of benign and malignant nodules were calculated, it ranged from (1.5 to 6.6) in benign lesions of mean (3.7 ± 1.1) and (1.7 to 4.2) of mean (3.2 ± 0.46) in malignant nodules as shown in [table 8], area under curve was 0.415, p value was also insignificant.

ADC value was calculated for both benign and malignant nodules, the range of ADC values for benign thyroid nodules were 1.86 ± 0.82 and 0.5 to 1.5; respectively; p value was significant .

ROC curve analysis was done to determine optimum thresholds for discrimination between benign and malignant lesions based on ADC values it was about 0.8 **(Figure 1)**.

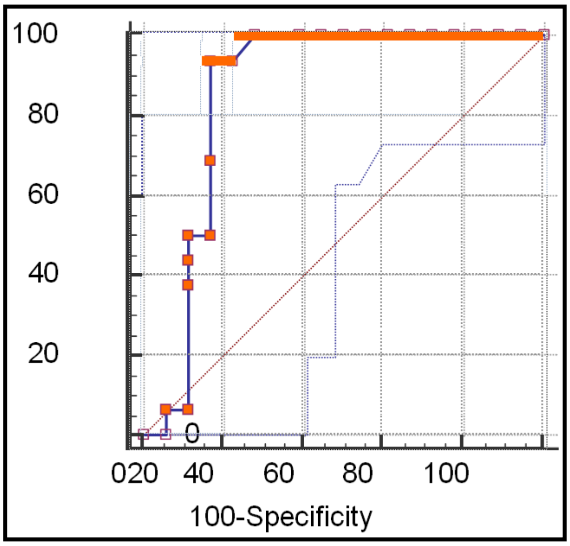

Figure (1): ROC curve for detection of malignancy using ADC

Cut off value was established it measured 1.2 with 93% sensitivity and 83% specificity as demonstrated in. (**Table 6)**

Table (6): Cut off value, sensitivity and specificity of ADC value

Area Under the Curve	P value	95% Confidence Interval		
		Cut off	Sensitivity %	Specificity %
0.820	<0.0001	<1.2	93	83

DISCUSSION

MRI signal intensity characteristics of thyroid lesions may be able to discriminate between different types of thyroid lesions, potentially improving clinical management. Also various studies have assessed the power of diffusion-weighted imaging (DWI) and its quantitative counterpart apparent diffusion correction (ADC) for differentiation between benign and malignant thyroid nodules. The results of these studies have been promising but wide variability has been encountered. It is a noninvasive and complimentary tool in the assessment of thyroid nodules. DWI can lower the burden of unnecessary surgery in cases with inconclusive pathology *(Bozgeyik et al., 2013).*

The purpose of our study was to determine the diagnostic role of diffusion-weighted imaging (DWI), ADC, T1 and T2 SIR values in the differentiation of malignant and benign thyroid nodules by using fine needle aspiration biopsy cytology criteria as a reference standard *(Bozgeyik et al., 2013).*

DWI may be a routine sequence in oncologic settings and it provides much useful information about tumoral tissue. It can be added to conventional MRI sequences. The most prominent advantages of this technique are absence of radiation, no necessity for of intravenous contrast material, very quick technique and quantitative information of tissue provided by ADC measurement *(White et al., 2014).*

Generally, the ADC values of the malignant nodules were reported to be significantly lower than those of benign thyroid nodules, attributed to cellular density and blood perfusion to the tissue. Malignant nodules of thyroid have compact cellularity, nucleocyte–cytoplasmic ratio, and usually cell membrane, which results in restriction in Brownian motion of water molecules in extracellular space and leads to decreased ADC value *(Bozgeyik et al., 2013)*.

In our study, evaluation of the ADC values following using b factors 0, 400, and 800 mm2/s revealed high mean values for benign thyroid nodules and reduced mean values for malignant thyroid nodules. The cut off value for differentiating malignant thyroid nodules from benign nodules was significant.

Khizer et al. (2015) stated that thyroid gland nodules. DWI was done using b-values of 0 and 1000 s/mm2and ADC values were calculated for the thyroid nodules. All of these patients were subjected to ultrasound guided core biopsy and histopathology results were correlated with ADC values. The benign nodules showed facilitated diffusion while malignant nodules showed restricted diffusion. The mean ADC value of the malignant thyroid nodules (0.94 ± 0.16 x 10- 3mm2/s) was significantly lower than that of the benign thyroid nodules (1.93 ± 0.13 x 10-3mm2/s) (p-value =0.05). ADC value of 1.6 x 10-3mm2/s was used as a cut-off, for differentiating benign from malignant thyroid nodules.

This wide variability in between various studies might be justified by heterogeneity in the design of studies, especially regarding b factors. Heterogeneity of thyroid neoplastic cellular types might also contribute to this variability. *Ilica et al. (2013)* showed an ADC cutoff value of 0.9 × 10- 3 mm2/s results in sensitivity and specificity of 90% and 100%, respectively, for differentiation of malignant and benign thyroid lesions; however, the study was limited by small number of participants. Several studies have proposed b value of 300 to be enough for characterization of thyroid nodules; however, according to the Meta analysis of using higher b value improves the strength of DWI for characterization of thyroid nodules. Using low b factor might lead to inaccurately high ADC value *(Chen et al. 2016; Aghaghazvini et al., 2018)*.

MRI T1 and T2 signal intensity ratios (SIR) could probably assist in differentiation between and malignant thyroid nodules; *Noda et al. (2015)*, in a study on the significance of SIR T1, SIR T2 and ADC values in differentiation between benign and malignant papillary thyroid cancer, the quantitative image analysis revealed that the mean SIR of axial TSE T1-weighted imaging of benign nodules and malignant nodules of insignificant value. The mean SIR of axial TSE T2-weighted imaging of benign nodules was significantly higher than malignant thyroid nodules. They had explained that the cause of this significance is related to the pathology of the papillary of thyroid cancer under microscope, i.e. high cellularity and fibrous component, which is not the case in other types of malignant thyroid nodules.

However, in our study after comparison between the SIRT1 and SIR

T2 values of the benign and malignant thyroid nodules the signal intensity ratio (SIR) of T1weighted images ranges for both benign and malignant thyroid nodules about of insignificant which agreed with the fore mentioned study. Signal intensity ratio (SIR) of T2 weighted images ranges for both benign and malignant thyroid nodules about and of insignificant value, which was different from this study. This might be attributed to the small number of the malignant nodules in our study specifically the papillary malignant subtype.

The T2 SIR, although it is not significant, it can be used to evaluate the morphological structure of thyroid pathology and to detect pathologically looking cervical lymph nodes; combined T2 SIR and ADC may yield higher diagnostic performance as it helps choosing proper areas for ADC measurement away from cystic areas. Moreover, although T1-weighted imaging was not significant in the differentiation of malignant and benign thyroid nodules, the previous studies convey that T1-weighted imaging (even if not significant) may play a supportive role in detecting hemorrhage or calcification within thyroid nodules.

CONCLUSION

DWI provided very useful and promising results on the nature of a thyroid nodule. These results may have a role in the selection of nodules that are going to undergo FNAC. However, although these are promising results, further investigations are needed with larger patient groups.

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دور الرنين المغناطيسى بالانتشار فى حالات التضخم العنقودى للغدة الدرقية

شوقى دعبس، محمد الشافعى، هيثم محمود نفادى*، هيثم أحمد شحاته فتح الباب

قسمى الجراحة العامة والأشعة التشخيصية*، كلية الطب، جامعة الأزهر، القاهرة

الناشر: هيثم احمد شحاته فتح الباب، **تليفون:** 01224378613،

E-mail: drhaythm48@gmail.com

خلفيـــة البحـــث: يعتبـــر التضـــخم العنقـــودى للغـــدة الدرقيـــة أحـــد الاضـــطرابات الأكثـــر شـــيوعاً التـــى تصـــيب الغـــدة الدرقيـــة. وفـــي مصـــر، يحـــدث تضـــخم الغـــدة الدرقيـــة العقـــدي بنســـبة تتـــراوح بـــين 4٪-7٪ مـــن الســـكان. وقـــد تكـــون تقنيـــات التصـــوير الإشـــعاعي الجديـــدة واعـــدةً للتشـــخيص التفريقـــي لعقيـــدة الغدة الدرقية.

الهـــــدف: تحديـــد الـــدور التشخيصـــي للـــرنين المغناطيســـى بالانتشـــار فـــي التمييـــز بـــين العقيـــدات الدرقيـــة الخبيثـــة والحميـــدة باســـتخدام دراســـة التشـــريح المرضي كمعيار مرجعي.

المرضـــى وطـــرق البحـــث: شـــملت الدراســـة 35 مريضـــاً (28 مـــن الإنـــاث و 7 مـــن الـــذكور)، تتـــراوح أعمـــارهم بـــين (12 ســـنة إلـــى 75 ســـنة) بمتوســـط عمـــر 48.65 (.7 14.72). وقـــد تـــم إحالـــة جميـــع المرضـــى إلـــى قســـم الجراحـــة بمستشـــفى الحســـين الجـــامعي خـــلال الفتـــرة مـــن يوليـــو 2018 إلـــى أغسطس 2019 مع توسيع الغدة الدرقية.

نتـــائج البحـــث: فـــي دراســـتنا، كـــان هنـــاك 7 (60.6 ٪) ذكـــور و 28 (79.4 ٪) إنـــاث فـــي مجموعـــة المرضـــى. كانـــت نســـبة العقيـــدات الدرقيـــة الحميـــدة 52.9 ٪. كانـــت النســـبة المئويـــة للعقيـــدات الدرقيـــة الخبيثـــة 47.1 ٪. تـــم حســـاب قيمـــة معامـــل الانتشـــار الظـــاهري لكـــل مـــن العقيـــدات الحميـــدة

والخبيثـــة، وكـــان نطـــاق قـــيم ADC للعقيـــدات الدرقيـــة الحميـــدة (0.03 إلـــى 3.5) مـــــن المتوســـــط (1.86 ± 0.82) و (0.5 إلـــــى 1.5) مـــــن المتوســـــط (1.04 ± 0.2) ، كانـــــت قيمـــــة p مهـــم (<0.0001) مـــع قيمـــــة مقطوعـــــة 1.2 مع حساسية 93 ٪ وخصوصية 83٪.

الاســـتنتاج: يـــوفر الـــرنين المغناطيســـي بالانتشـــار نتـــائج مفيـــدة واعـــدة للغايـــة فـــى حـــالات التضـــخم العنقـــودى للغـــدة الدرقيـــة. وقـــد يكـــون لهـــذه النتـــائج دور فـــي اختيـــار العقيـــدات التـــي كانـــت ستخضـــع FNAC. وعلـــى الـــرغم مـــن أن هـــــذه النتـــــائج واعـــــدة، إلا أن هنـــــاك حاجـــــة لمزيـــــد مـــــن الدراســـــات مـــــع مجموعات أكبر من المرضى.

الكلمـــات الدالـــة : الانتشـــــار – التـــردد المغناطيســـى – حبيبـــات الغـــدة الدرقيـــة .