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Orginal Article

Diagnostic Efficacy of Ultrasound, Diffusion-Weighted Magnetic Resonance Imaging and Apparent Diffusion Coefficient values in Thyroid Nodules

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ABSTRACT

Background: US is widely used in the assessment of the thyroid gland. Thyroid nodules may be benign or malignant. This study aimed to assess the great role of US, DW-MRI and ADC values in assessment of thyroid nodules and to reduce cost-effectiveness by decreasing number of unnecessary FNAC. **Methods**: Sixty-two patients with seventy-three thyroid nodules were included in a prospective study (seven males and fifty-five females). Sixty patients were new cases of thyroid nodules and two cases were recurrent cases post total thyroidectomy. Thyroid ultrasound was done to all patients. The nodules were classified into TIRADS categories. According to TIRADS, they were classified into groups **A** & **B**. The patients in group **B** performed DW-MRI examination. **Results**: Six nodules out of seventy-three were malignant. Malignant nodules were two in TIRADS **3**, one in TIRADS **4b**, two in TIRADS **5** and one in recurrent thyroid nodules. The major US features seen associated with malignancy were microcalcifications, hypoechoic echo pattern & irregular borders. Twelve patients with sixteen nodules performed DW-MRI and ADC value measurement. Eleven nodules showed free diffusion with higher ADC values and five nodules showed restricted diffusion with lower ADC values. On comparison with histopathology, four nodules with restricted diffusion & lower ADC values were proven to be malignant. So DW-MRI has high sensitivity (91.7%) and specificity (100%) in differentiating benign and malignant thyroid nodules. **Conclusions:** Combining US features, DW-MRI and ADC values could improve the diagnostic performance of US and MRI for malignant thyroid nodules. **Key words:** Ultrasonography; Magnetic Resonance Imaging; thyroid nodules.

INTRODUCTION

Ultrasonography (US) is widely used in the assessment of the thyroid gland. Among the different pathologies that can be depicted and characterized by US are nodules. Nodules may be benign or malignant. Some studies have shown that less than 10% of thyroid nodules are malignant and that thyroid US depicts nodules in up to 50% to 67% of the population [1,2]. Although ultrasound (US) is widely used to detect thyroid nodules and determine their malignant potential, the US features and index of each grade of Thyroid Imaging Reporting and Data System (TI-RADS) remain controversial[3,4].US guided fine needle aspiration biopsy (FNAB) is widely used for the diagnosis of thyroid nodules [4]. However, up to 7% of the nodules yield non diagnostic cytology and an additional 15-30% of fine needle aspiration cytology (FNAC) show an indeterminate cytology [4,5]. MRI signal intensity characteristics of thyroid lesions can enable us to differentiate the different types of thyroid lesions, potentially improving clinical management [3]. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a recent addition to the MR sequences. It can provide qualitative and quantitative functional information concerning the microscopic movements of water at the cellular level [6].

AIM OF THE WORK

The study aimed to assess accuracy of US, Doppler, DW-MRI and ADC value measurement in assessment of thyroid nodules using pathological examination as a golden standard.

PATIENT AND METHODS

PATIENT: This prospective study was conducted at Radiology Department; Zagazig University during the period from November 2018 to February 2020. The study included sixty-two patients (seven males and fifty-five females); Their ages ranged from 18 to 72 years old with the mean of age 43.19 ± 15.11. Informed consent had been taken from all the participants in this study. This study was approved by Institutional Review Board (IRB) of faculty of medicine, Zagazig university. The patients were divided into two groups according to TIRADS categories of their thyroid nodules; **Group A**, including fifty patients who were classified as TIRADS 2 and 3 (subjected to US and histopathological examinations) & **Group B**, including twelve patients who were classified as TIRADS 4A,4B and 5 in addition to patients with recurrent thyroid nodules after prior total thyroidectomy (subjected to US, MRI and histopathological examinations). Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patient inclusion criteria: All patients complaining of lump in the neck, neck pain, difficulty of swallowing, hoarseness of voice, swollen neck lymph nodes or enlarged thyroid gland. **Patient exclusion criteria:** Patients unwilling to complete the study. Any person incompatible with MRI or its contrast.

METHODS: All Patients were subjected to Complete history taking, full clinical examination**,** thyroid ultrasonography and color Doppler evaluation**.** Twelve patients with sixteen nodules were subjected to MRI evaluation (T1WI, contrast enhanced fat suppressed T1WI, T2WI, DWI using b value 800s/mm2, ADC map). Thirty-five patients were subjected to FNAC nearly four weeks after radiological examination. Twenty-five patients underwent total thyroidectomy. Two patients were subjected to FNAC then underwent thyroidectomy. Pathological examination was performed to all FNAC smears and thyroidectomy specimens.

ULTRASONOGRAPHIC TECHNIQUE:

All ultrasound scans of the thyroid gland and neck areas were performed using Toshiba aplio 500 ultrasound systems. With a 7.5-10 MHz high frequency linear array transducer. All images were examined on real-time two-dimensional gray-scale and Doppler imaging. Both lobes of the thyroid gland and the isthmus were evaluated. Patients were scanned in the supine position with the neck mildly hyperextended by an "oatmeal" pillow. The neck was scanned in sagittal, transverse, and oblique sections to optimally visualize both thyroid lobes, isthmus, carotid arteries and internal jugular veins. Imaging of the lower poles of thyroid lobes was improved by making the patient swallow. This aided to raise the thyroid gland in the neck. The region of the carotid artery and jugular veins laterally and supraclavicular fossa were also examined for any lymphadenopathy. All thyroid nodules were characterized according to the internal component (solid, mixed or cystic), the margins, echogenicity, evidence of calcifications and the shape. Margins were assorted as well defined, ill-defined or irregular. Echogenicity was assorted as an echogenicity, hyper- echogenicity, iso echogenicity, hypo echogenicity and marked hypo echogenicity. Iso echogenicity was defined as an echogenicity similar to that of the adjacent healthy thyroid gland. A nodule was assorted as “marked hypo echogenicity” if the echogenicity was less than that of the superficial surrounding neck muscles. When present, calcifications were classified as microcalcifications (<1 mm) and macrocalcifications (>1 mm with acoustic shadowing). The shape of the nodule was assorted as taller-than-wide (greater in its antero-posterior dimension than in its transverse dimension) and wider-than-tall (ovoid to round). Vascularity using color Doppler ultrasonography, was categorized as absent, peri nodular or intra nodular. Using the modified Russ classification **[7]**, each nodule was classified into a TIRADS category (1, 2, 3, 4A, 4B and 5) based on the US features. TI-RADS 1 corresponds to a normal gland, TI-RADS 2 is a benign nodule, and TI-RADS 3 is a highly probable benign nodule. Suspicion of malignancy can be divided into three categories: TI-RADS 4A and 4B correspond to low and high suspicion for malignancy respectively, whereas TI-RADS 5 corresponds to a malignant nodule with more than two criteria of high suspicion and/or suspicious cervical lymph node. These malignant criteria are: marked hypo-echogenicity, taller than wide shape, irregular margin and presence of microcalcifications within the nodule.

MRI TECHNIQUE:

MRI was performed using a Philips 1.5-T MRI system. 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: 544/19 &3-4 mm section thickness with a 3-4 mm intersection gap), fat suppressed T1-weighted imaging (TR/TE:300/406 &4 mm section thickness with a 4 mm intersection gap), T2-weighted turbo spin echo imaging (TR/TE:6340/88&3-4 mm section thickness with a 3-4 mm intersection gap), diffusion-weighted single-shot turbo spin-echo echo-planar imaging (TR/TE: 7020/180, b factors: 50-800 s/mm2&3-4 mm section thickness with a 3-4 mm intersection gap), ADC maps were reconstructed. According to **Erdem et al., [8]**, we considered the mean ADC values of thyroid nodules were 2.745.3 ± 0.601 $x10^{-3}$ mm2/s in the benign group and 0.6952±0.3125 $x10^{-3}$ mm2/s in the malignant group. For each measurement of the ADC value, a circular ROI cursor drawn to encompass the area of lowest ADC map signal intensity within the nodule accurately excluding artifacts or cystic portions of thyroid nodules. The ADC value for each case was compared to the result of the cytological examinations being positive or negative for malignancy. Contrast enhancement studies were implemented using axial T1WI obtained with a fast-spoiled gradient recalled echo (TR/TE, 544 ms/19 ms&3-4 mm section thickness with a 3-4 mm intersection gap). Gadolinium (Magnevist) was intravenously injected at 0.2 ml/kg body weight and 3 ml/s, followed by a 20 ml saline flush. In the contrast-enhanced protocol, breath-hold was performed.

ULTRASOUND-GUIDED FNAB:

The cases were indicated to undergo fine needle aspiration cytology from the thyroid nodules. The cases were referred to the interventional radiology unit in Radiology Department in Zagazig University. The Thyroid functions and bleeding profile tests were done (with accepted INR level up to 1.4 and platelet count above 50.000/mL) then the cases were scheduled for ultrasound-guided FNAC. The suspicious nodules were localized and aspirated under US guidance by 20-22G needle in the availability of a cyto-pathologist to obtain and properly handle the aspirated material. Two or three aspirates were performed.

STATISTICAL ANALYSIS:

All data were analyzed using Statistical Package for Social Sciences (SPSS) 23 for windows. Numerical data were summarized using means and standard deviations or medians and ranges, as appropriate. Categorical data were summarized as numbers and percentages. Numerical data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. The estimation of the cutoff value, sensitivity, specificity for differentiation between the negative and positive for malignancy were performed using the ROC curve. All p-values are two-sided. P-values<0.05 were considered significant.

RESULTS

The current study included seventy-three nodules out of sixty-two patients who fulfilled the inclusion criteria selected for the study. There were fifty-two patients with solitary thyroid nodule and ten patients with multiple nodules (one patient had three nodules and nine patients had two nodules). Male constituted 11.3% of the studied patients with age ranged from 18 to 72 years. Larger percentage of nodules were TIRADS 3 followed by 2 then 4b **Table (1)**. About 69% and 63% of the nodules in group B had free diffusion and mild enhancement in MRI imaging of nodules with ADC value ranged from 0.7 to 2.9 $x10^{-3}$ mm2/s. **Table (2)**. The best cutoff value of ADC in prediction of benign nature of nodule was ≥0.85 $x10^{-3}$ with area under curve 0.952, sensitivity 90%, specificity 75%, positive predictive value 90%, negative predictive value 75% and accuracy (85.7%) **Figure (1)**. MRI results showed better sensitivity, specificity, PPV, NPV and accuracy values in the prediction of benign nature of thyroid nodules. **Table (3)**.

Table (1): Distribution of the studied nodules according to TIRADS.

TIRADS	N=73	%
T 2	12	16.4
T 3	45	61.6
T 4a	3	18.8
T 4b	9	4.1
T 5	2	2.7
Recurrent	2	2.7

Table (2) : Distribution of the studied nodules according to MRI findings

		N= 16 (%)
Diffusion	Free	11 (68.8)
	Restricted	5 (31.2)
ACD	Mean + SD	1.729 + 0.795 mm2 |sec.
	Range	0.9-2.9 x10-3mm2 |sec
Enhancement	Moderate	6(37.5)
	Mild	10 (62.5)

Table (3): Results of US Vs results of MRI in the prediction of benign nature of thyroid nodules in group B.

		Sensitivity value %	Specificity value %	PPV value %	NPV value %	Accuracy value %
U.S.	Well-defined margin	83.3	50	83.3	50	75
	Oval shape	91.7	0	73.3	0	68.8
	Hypoechoic halo	8.3	100	100	26.7	31.25
	Iso-echogenicity	25	100	100	30.8	43.8
	Solid nature	83.3	0	71.4	0	62.5
	Absent micro-calcification	16.7	100	100	28.6	37.5
	Absent or peri nodular vascularity	58	75	87.5	37.5	62.5
MRI	Free diffusion	91.7	100	100	80	93.8
	ADC cut off value≥0.85 *10-3	90	75	90	75	85.7
	Mild enhancement	83.3	100	100	66.7	87.5

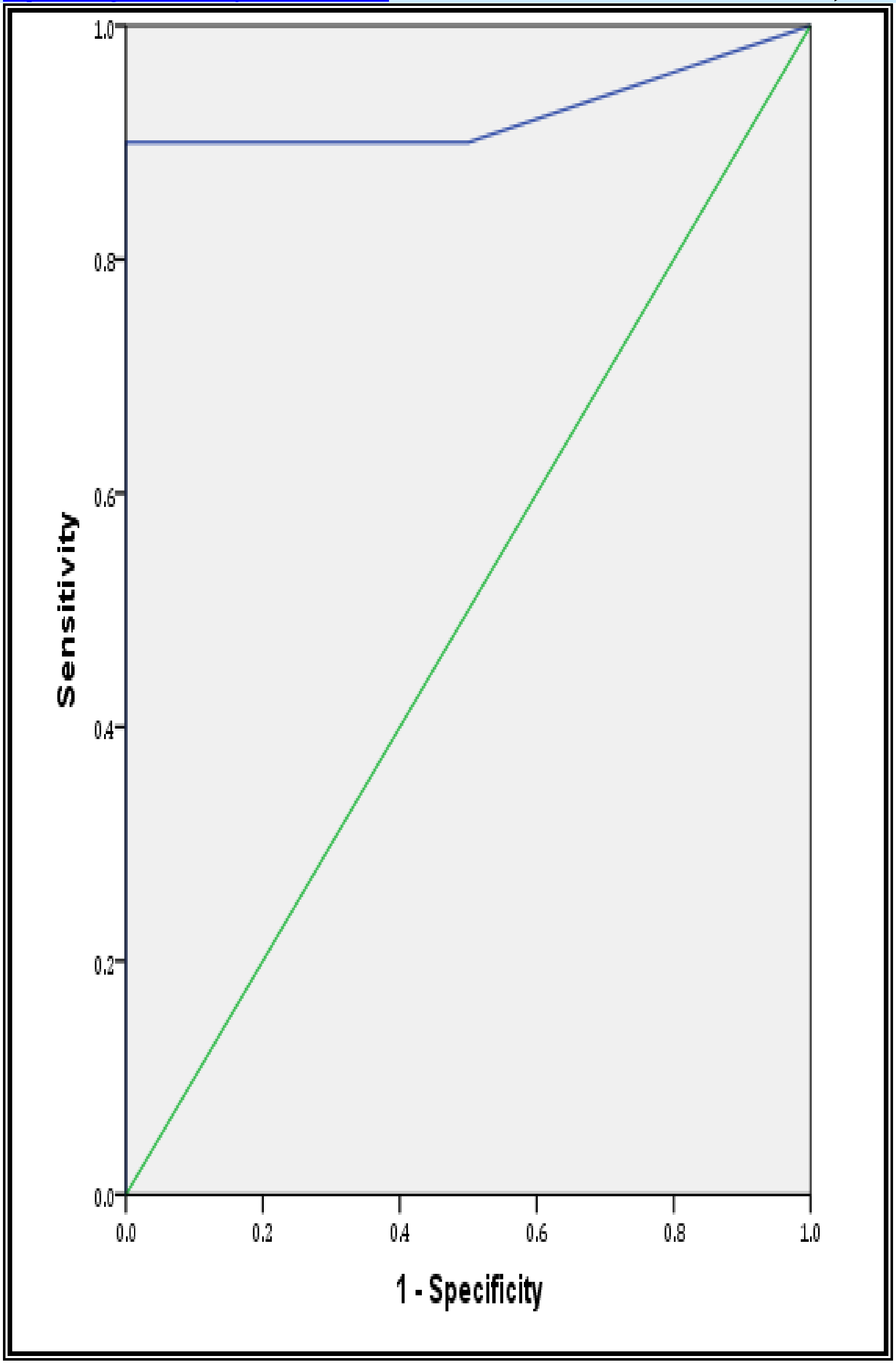

Figure (1): ROC curve showing performance of ADC in prediction of benign nature of nodule.

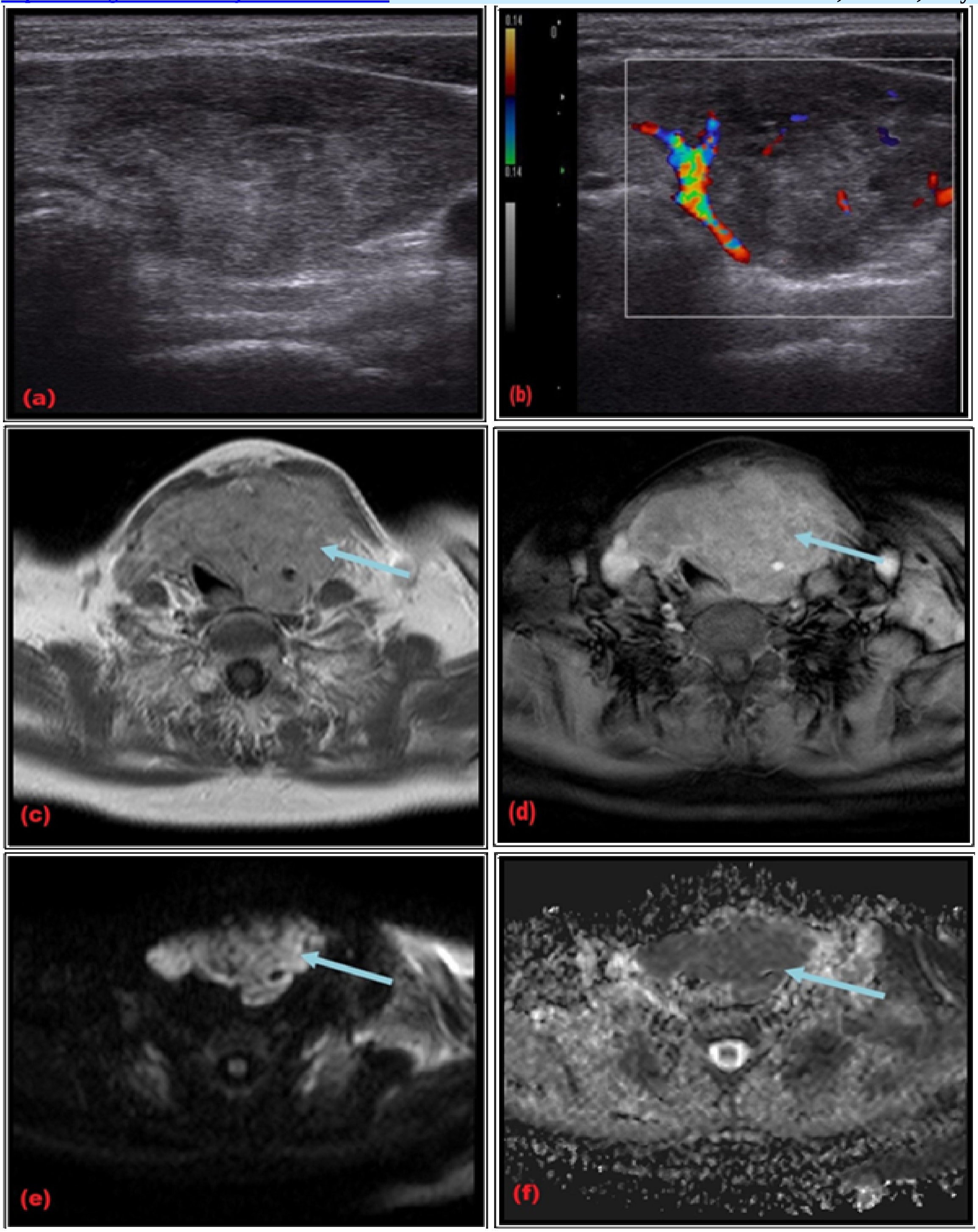

Figure (2): female patient 62 years old presented with neck swelling. **(a)** There is a left thyroid lobe hypoechoic mass which is wider than taller with irregular margins and internal microcalcifications on grayscale US. **(b)** It shows peri nodular and intra nodular vascularity on color doppler flow. **(c)** On T1WI, the mass appears of intermediate signal intensity. **(d)** The mass shows homogenous enhancement on post contrast T1WI. **(e)** The mass shows restricted diffusion that appears as high signal intensity on DWI. **(f)** The mass appears of low signal intensity on ADC map. The ADC value was 0.7 x10−3 mm2/s suggested to be malignant. The final diagnosis is papillary thyroid carcinoma.

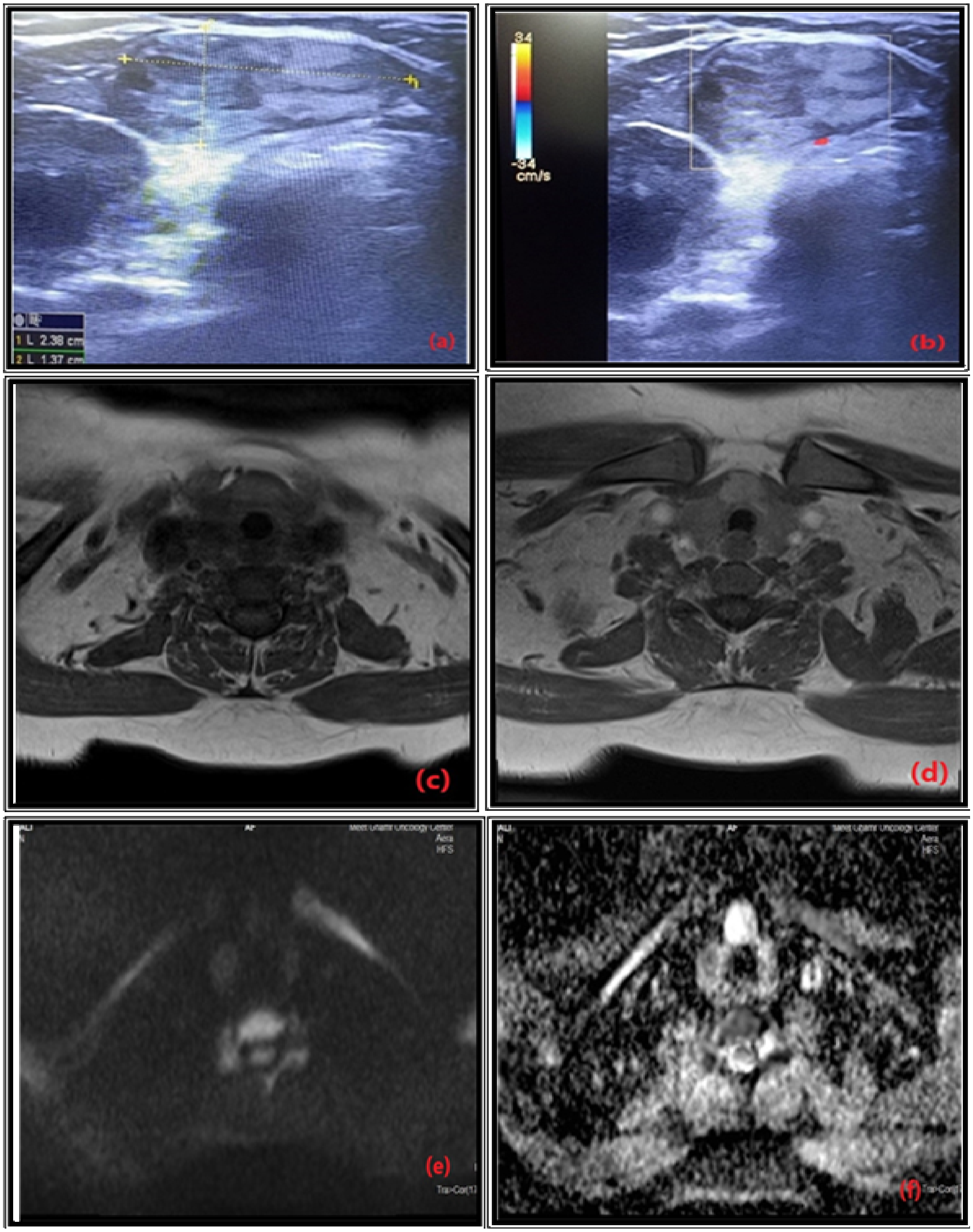

Figure (3): Female patient 48 years old presented with swallowing and breathing difficulties. **(a)** There is an isthmic nodule of mixed echogenicity which is wider than taller with well-defined margins on grayscale US. **(b)** The nodule shows peri-nodular vascularity on color doppler flow. **(c)** On T1WI, the nodule appears of high signal intensity. **(d)** The nodule shows homogenous enhancement on post contrast T1WI. **(e)** The nodule shows free diffusion that appears as low signal intensity on DWI. (f) the nodule appears of high signal intensity on ADC map. **(f)** The ADC value was 2 x10−3 mm2/s suggested to be benign. The final diagnosis is multinodular goitre.

DISCUSSION

Women are more prone to thyroid problems than men **[9]**. Our study included sixty-two patients; 88.7% were females while 11.3% were males. The majority of patients were between 25 and 55 years of age. These results are in the same line with **Aimel et al. [10]** ,who found a male-to-female ratio of 1:3. Thyroid cancer is a rare entity to some extent, with an estimated prevalence of about 5%[11]. The proportion of malignant thyroid nodules obtained in our study was exceeding that value (**8.2%**), however it was less than that obtained by **Moon et al.,[12]** in 2012 (**30.8%**). From our results, the risk of malignancy significantly increased from TI-RADS 3 to 5. This was zero for TI-RADS 2. In his work, Horvath suggested a malignant risk of less than **5%** for TI-RADS 3[13]. Our findings (**2.7%**) are within this range suggested by Horvath and more than that obtained by Russ et al., (**0.25%**). **Russ et al., [7]** showed a malignant risk of about **6%** for TI-RADS 4A and in our study it was **0 %** and this may be attributed to small number of nodules in ours. For TI-RADS 4B Russ et al., showed **69%** risk of malignancy and in our study, it was **1.4%** less than that obtained by Moifo et al., (**57.9%**) and less than that suggested by Horvath et al., (**10-80%**) due to the few numbers of TIRADS 4B nodules in our study. Finally; all TNs in TI-RADS 5 category in our study proved to be malignant (**100%**), similar to that of Russ et al., and **Moifo et al.,[14]** (**100%**) but Horvath et al., and **Kwak et al., [11]** reported for this category a probability of malignancy of **85-99%**.Most cancers were found in the TI-RADS **3, 4B** and **5** categories. We can infer from this that most cancers will have US characters suspicious for malignancy. There were four signs of high suspicion, confirming repeated findings in the literature of the past 10 years: Irregular borders, microcalcifications, marked hypo-echogenicity and taller than wide shape. In our study, irregular margins, hypo-echogenicity and microcalcifications were found to be highly suspicious for malignancy. In **Moifo et al., [14]** study, **21%** of malignant nodules did not have suspicious malignant characters on US and were categorized as TI-RADS 3. Also, in our study **33.3%** of malignant nodules were classified as TI-RADS 3. DWI can provide a non-contrast MRI alternative for the characterization of soft tissue masses**.** DWI has proven usefulness for the evaluation of tumor cellularity in soft-tissue tumors and can be used as a powerful noninvasive tool to assess changes in tumor cellularity [15]. In our study we considered that the mean ADC values of thyroid nodules were 2.745.3 ± 0.601 mm2/s in the benign group and 0.6952±0.3125 mm2/s in the malignant group according to **Erdem et al., [8]**. In our study a comparison between the results of the ADC values and cytological examinations for the thyroid nodules was performed. The analysis of data revealed that the benign thyroid nodules exhibited ADC values equal to 2.11±0.719 mm2/s (mean ± standard deviation) while the malignant thyroid nodules exhibited ADC values equal to 0.775±0.0829 mm2/s (mean ± standard deviation). The statistical analysis revealed that the ADC cutoff value between the benign and malignant nodules is equal to 0.85 $x10^{-3}$mm2/s (p value< 0.05) the sensitivity was 90%, the specificity was 75%, PPV was 90%, NPV was 75% and the accuracy was 85.7%for this cut off value for b value 800 s/mm2. Our results were in the same line with **Mutlu et al. [16]**who found in their study that the sensitivity, specificity, PPV, NPV and accuracy rates for ADC values in discriminating benign and malignant thyroid nodules were calculated as 80% ,97% ,80% ,97% ,96% respectively for b values 50,400 and 1000 s/mm2 when using the cutoff value of $1.0x10^{-3}$ mm2/s. Our results were not on the same line with **El-Hariri et al.**[17] who found in their study that the sensitivity ,specificity ,PPV and NPV for ADC values in discriminating benign and malignant thyroid nodules were calculated as 94% ,95% ,94% and 95% respectively for b value 500 s/mm2 when using the cutoff value of $1.5x10^{-3}$ mm2/s. Also **Nakahira et al.[18]** found that a cut off value for malignant nodules of 1.6 x 10^{-3} mm2/s yielded sensitivity ,specificity and accuracy of 94.73%,82.60% and 88.09 % respectively for b value 1000 s/mm2. Different studies showed variation in the cutoff values for predicting thyroid carcinoma, so each MRI unit should determine the precise threshold value for predicting malignancy in thyroid nodules as there are variations in MRI systems ,coils and pulse sequences [19]. Contrast enhanced MRI provides information concerning the vascularity of lesions. The degree of enhancement represents the degree of vascularity [20]. In our study, blood vessels, thyroid tissue, and muscles were used to evaluate subjectively the degree of early enhancement of the nodule, which was classified as: **Mild** (the enhancement was similar to that of adjacent muscle tissues); **Moderate** (the enhancement was higher than that of adjacent muscle tissues but lower than that of blood vessels); & **Marked** (the enhancement approached that of blood vessels). Nodular goiter and colloid nodules showed mild degree of enhancement. Benign follicular lesion and follicular neoplasm showed moderate degree of enhancement. Papillary carcinoma showed moderate degree of enhancement. Medullary carcinoma showed moderate degree of enhancement, which were consistent with previous studies [21].

CONCLUSIONS

Combining ultrasonographic features to DW-MRI and ADC values measurement could improve the diagnostic performance of US and MRI for malignant thyroid nodules.

Conflict of Interest: Nothing to declare.

Financial Disclosures: Nothing to declare.

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