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Original Article

Radiology Section

Role of Diffusion Weighted Magnetic Resonance Imaging in Differentiating Benign From Malignant Thyroid Lesions: A Prospective Study

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ABSTRACT

Introduction: Accurate non-invasive imaging technique for characterising thyroid nodules has always been problematic. Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) is a functional MR imaging modality that quantifies the net diffusion of water molecules in any lesion. Thyroid carcinoma due to its increased cellularity shows diffusion restriction on DWI with low Apparent Diffusion Coefficient (ADC) values that can be used to differentiate benign and malignant thyroid nodules.

Aim: To evaluate role of DW-MRI in differentiating benign from malignant thyroid disease and to calculate ADC values of thyroid lesion/nodule on DW-MRI and correlate with FNAC/histopathology findings.

Materials and Methods: A prospective study was conducted in department of Radiodiagnosis, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala. Total of fifty patients with neck swelling diagnosed clinically and confirmed on ultrasound were included. The patients underwent routine as well diffusion weighted MRI using b-values of 0,400 and 800 mm^2/sec. Their ADC values were calculated and were finally correlated with histopathological findings. Statistical analysis was done using SPSS v.21 and a p-value of <0.05 was considered as significant.

Results: The mean age of the patients was 41.8±13.9 years with maximum number of patients in the age group of 31 to 40 years. The mean ADC value of benign thyroid nodules ($1.721\times10^{-3} mm^2$/sec) was significantly higher than that of malignant thyroid nodules ($1.075\times10^{-3} mm^2$/sec) (p=0.01). The best cut-off value for distinguishing benign and malignant nodules was $1.371\times10^{-3} mm^2$/sec with sensitivity, specificity, PPV an NPV of 93.75%, 91.17%, 83.33% and 96.87%, respectively. The accuracy of the study in differentiating benign from malignant thyroid lesions was 92%.

Conclusion: DW-MRI due to its ability to probe the microstructure of the tumour, its short acquisition time, its high repeatability and safety is a new promising non-invasive imaging modality that can reliably differentiate between benign and malignant thyroid nodules and can help avoid unnecessary biopsies and consequently its hazards.

Keywords: Apparent diffusion coefficient, b-value, Fine needle aspiration, Receiver operator characteristic curve

INTRODUCTION

The most common pathology of thyroid gland is thyroid nodules. There has been an increase in the incidence and prevalence of thyroid cancer [1-3]. The prevalence of thyroid disorders is 0.8% from total body malignancies. The prevalence is significantly higher in females than males and it was also higher in age group >31 years than age group <30 years [4]. USG is a sensitive and most common non-invasive diagnostic tool for thyroid lesions but there is still no reliable criteria to distinguish malignant and benign lesions and it is difficult to diagnose a malignant nodule if it is very large in size or is multinodular [5]. The use of colour doppler sonography to predict thyroid malignancy has given controversial results as some believe it to be helpful while others did not find it useful to improve diagnostic accuracy [5-8]. Fine Needle Aspiration (FNA) is considered as the diagnostic method of choice. However, the sensitivity of Fine Needle Aspiration Cytology (FNAC) is low due to factors like multiple nodules, experience of cytopathologist and indeterminate cytologic findings [9]. DWI is a non-invasive method with no risk of radiation which can differentiate benign and malignant lesions [10]. Benign or malignant lesion leads to microstructural changes in the tissue that produces different signals on DWI which can quantified by calculating ADC values.

Earlier, DW-MRI was mainly used for detection of cerebral ischemia in brain (hyperacute stage) but over the last two decades DW-MRI is now being used in other extracranial lesions [11,12]. Cancer is characterised by increased cellularity and hence shows restricted diffusion of water molecules. It has been seen that ADC is related to the cellular density of the tumours [11-13]. Most of the malignant tumours show reduced ADC due to high cellularity and reduced extravascular extracellular space [12]. Hence, ADC values calculation can distinguish malignant from benign thyroid nodules [13]. There is scarcity of literature in this field pertaining to Indian context [14]. Hence, the present study was carried out with an aim to determine the role of DW-MRI to diffferentiate between benign and malignant thyroid lesions and to analyse the ADC values from DW images and associate with Fine needle aspiration Cytology/histopathology.

MATERIALS AND METHODS

A prospective study was carried out from September 2017 to July 2019 in Maharishi Markandeshwar Institute of Medical sciences and Research, Mullana (Ambala). Hence, taking the study pertaining to sample size calculation for sensitivity and specificity, a sample size was calculated to be 40 [15]. To compensate for any inadequacy in data during study it was rounded off to 50. The study was approved by the local Ethics Committee vide no. 1076 and informed consent of the participants was obtained before the assessment. A total of 50 patients (37 females and 13 males) in the age group of 12 to 65 years referred from medicine, surgery or ENT OPD with clinically palpable thyroid nodule/nodules confirmed on ultrasound were included and Thyroid lesions <1 cm, patients with cochlear implant, pacemaker, intraocular metallic foreign body, uncooperative patients,

patients who are proven cases of thyroid malignancy and/or post-operative patients of neck surgery, patients who have diffuse enlargement of thyroid gland and patients with predominantly cystic component in the nodule were excluded from the study. A proper history was taken from all the patients. General and systemic examination was conducted thoroughly. Basic laboratory workup including complete blood count, chest x ray, thyroid function tests etc., was done.

MR scanning was performed with 1.5-T MR (Achieva, Philips Medical Systems, Netherland, B.V.) by using a standard head and neck coil. Localiser images was obtained in axial, coronal and sagittal planes followed by Conventional images including T2- weighted fast spin echo images (Repetition Time (TR)=3725 ms, Echo Time (TE)=80 ms) in axial and coronal planes, section thickness of 3 mm to 4 mm and intersection gap of 0.4 mm. Diffusion weighted MR images was obtained in axial plane with the parameters of Field of View (FOV)=250 mm, TR=3500 ms, TE=70 ms and 3 to 4 mm of slice thickness and 1 mm of intersection gap. A single shot echo-planar DW image was acquired using b-values (0, 400, 800) the diffusion sensitising gradient was applied in all three orthogonal planes (X,Y,Z) and Apparent Diffusion Coefficient (ADC) maps was automatically generated. ADC values were extracted from the ADC maps and were recorded.

A pilot project was conducted on a team of five radiologists who evaluated the DW images and calculated ADC values for a sample of 10 patients (who were not part of current study). The findings of the radiologists were scrutinized and unpaired t-test was applied to see the consensus among a pair of radiologists. The two radiologists who showed closest mean values and insignificant results on applying unpaired t-test were asked to participate in the study. These two experienced radiologists who were blind to the study independently, evaluated different set of DW images and calculated a single set of ADC value which was later correlated with FNAC/histopathological findings.

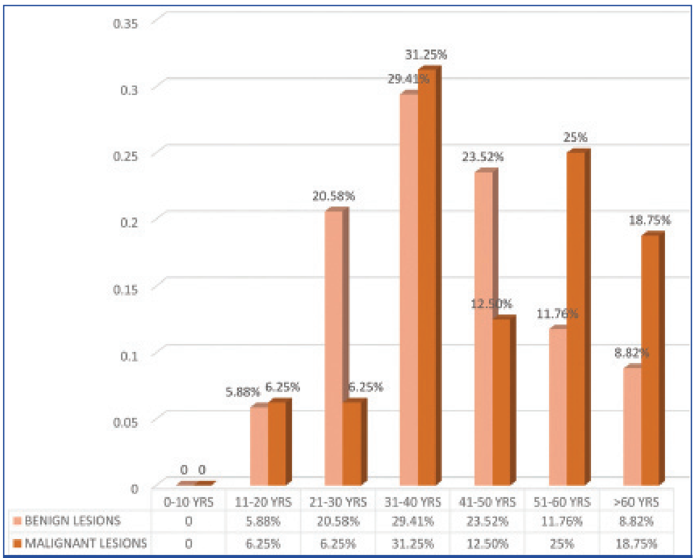
STATISTICAL ANALYSIS

Quantitative analysis was done using SPSS version 21. Diagnostic test sensitivity and specificity was obtained. Receiver Operating Characteristic (ROC) analysis curve was performed. A p-value <0.05 was considered significant.

RESULTS

Majority of patients were females 37 (74%) and only 13 (26%) patients were males. Most of the patients were in the age group of 31-40 years at presentation which were 15 (30% of the total cases). The youngest and oldest age at presentation was 12 years and 65 years, respectively. Mean age was 41.8±13.9 years (Range: 12-65 years) [Table/Fig-1]. Out of 50 patients in our study, 18 patients showed diffusion restriction on DWI and ADC value of less than $1.371 \times 10^{-3} mm^2/sec$ (cut-off value) and 32 patients showed no restriction on DWI and ADC value of more than $1.371 \times 10^{-3} mm^2/sec$.

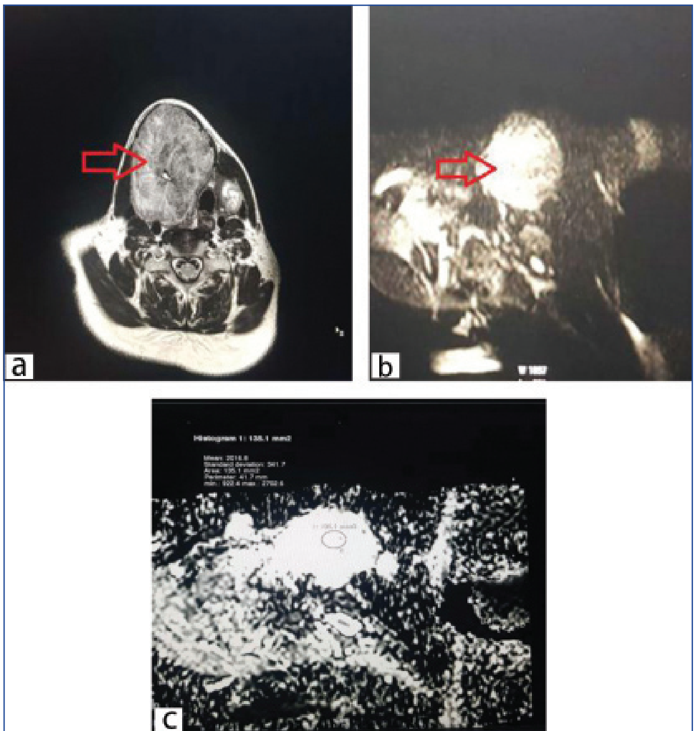
In final cytological/histopathological diagnosis of 50 patients, 34 patients had benign thyroid nodules and 16 patients had malignant thyroid nodules. Out of malignant thyroid nodules seven were papillary thyroid neoplasm, 3 were follicular neoplasm, three were medullary thyroid neoplasm, two were hurthle cell carcinoma and 1 was B-cell lymphoma of thyroid [Table/Fig-2]. On comparing with histopathological diagnosis, Out of 18 malignant lesions on DWI and ADC 15 were correctly diagnosed as malignant and three lesions were wrongly diagnosed which were benign on histopathology. And out of 32 benign lesions on DWI and ADC, 31 were correctly diagnosed as benign whereas one lesion was wrongly diagnosed which was malignant on histopathology. In present study of 50 patients, 34 patients had benign thyroid nodules on FNAC/Histopathological results with ADC value in the range of $0.602 \times 10^{-3} mm^2/sec$ to $2.408 \times 10^{-3} mm^2/sec$ with mean ADC value of $1.721 \pm 0.34 \times 10^{-3} mm^2/sec$ [Table/Fig-3]. Out of 16 malignant nodules with ADC value in the range of



[Table/Fig-1]: Bar diagram showing age wise distribution of benign and malignant thyroid lesions.

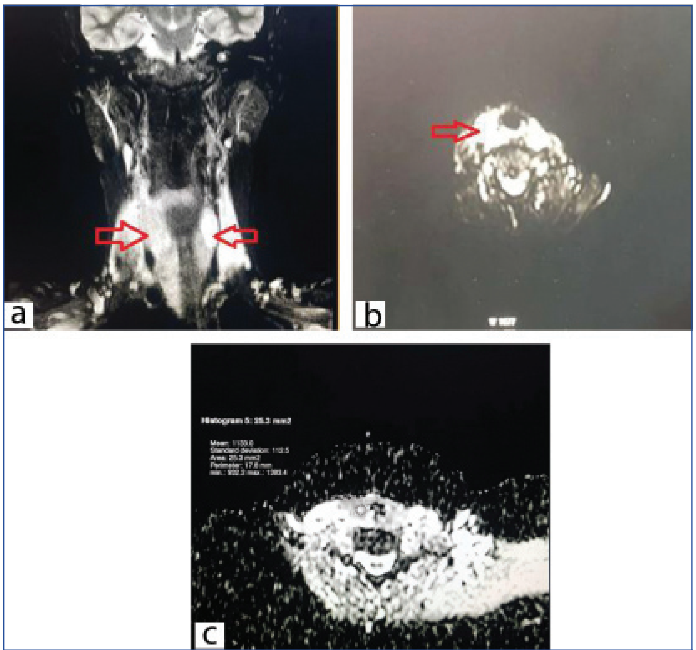
Final diagnosis	No. of Cases	% of Cases
Colloid Goitre	19	38%
Adenomatous Nodule	7	14%
Follicular Nodule	4	8%
Hyperplastic Nodule	3	6%
Hurthle Cell Adenoma	1	2%
Papillary CA	7	14%
Follicular CA	3	6%
Medullary CA	3	6%
Hurthle Cell CA	2	4%
B-Cell Lymphoma	1	2%
Total	50	100%

[Table/Fig-2]: Distribution according to histopathological/cytlogical diagnosis.



[Table/Fig-3]: a) Axial T2W image showing a large heterogeneously hyperintense lesion in right lobe of thyroid. Another small hyperintense lesion is seen within the right lobe of thyroid. b) DWI showing high signal within the lesion on right side c) ADC map showing high signal with an ADC value of $2.016 \times 10^{-3} mm^2/sec$ which was benign on MRI and proved to be multinodular goitre.

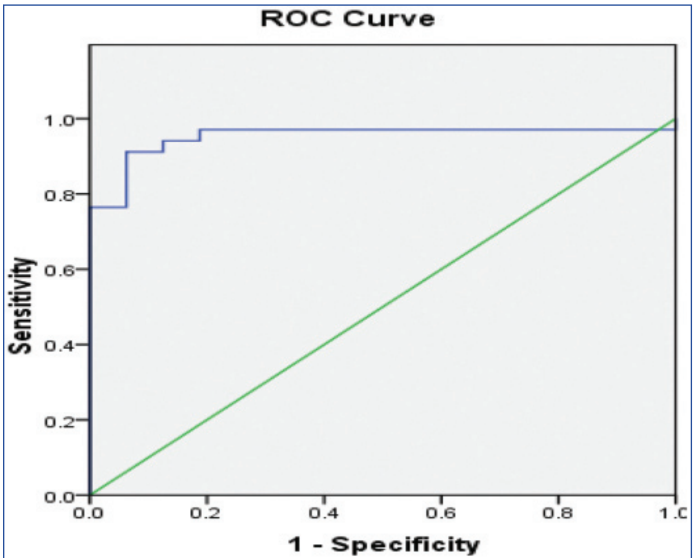
0.842×10^{-3} mm^2/sec to 1.512×10^{-3} mm^2/sec with mean ADC value was 1.075±0.197×10^{-3} mm^2/sec [Table/Fig-4]. The p-value of DWI for differentiating between benign and malignant lesions was 0.001. The calculated p-value was statistically significant and was less than 0.05 (Benign versus Malignant) [Table/Fig-5]. The ADC value of 1.371×10^{-3}mm^2/sec was used as a cut-off value for differentiation of benign from malignant thyroid nodules with a sensitivity of 93.75% and specificity of 91.17%, respectively [Table/Fig-6,7].



[Table/Fig-4]: a) Coronal T2W MRI shows hyperintense signal in the region of thyroid nodules on both sides.b) DW image shows hyperintense signal in both the lesions of thyroid. c) The lesion shows an area of low signal on ADC map with an ADC value of 1.13 x 10^{-3}mm^2/sec, which was malignant on MRI and proved to be follicular carcinoma of thyroid on HPE.

Final diagnosis	N	Mean (x 10^{-3} mm^2/ sec)	Std. devi-ation	95% Confidence Interval for Mean		Minimum (x 10^{-3} mm^2/sec)	Maxi-mum (x 10^{-3} mm^2/sec)	p-value
				Lower bound	Upper bound			
Benign	34	1.721	0.341	1.602	1.84	0.602	2.408	
Malignant	16	1.075	0.197	0.971	1.181	0.842	1.512	0.001
Total	50	1.515	0.427	1.393	1.636	0.602	2.408	

[Table/Fig-5]: Correlation of ADC values on DWI with FNAC/HPE diagnosis.



[Table/Fig-6]: Receiver Operator Characterstic (ROC) curve of ADC value for discrimination between benign and malignant thyroid nodules.

DISCUSSION

In present study, DWI was performed using b-values of 0, 400 and 800 mm^2/sec and a high quality image was obtained. ADC values of thyroid lesions were calculated. Mean ADC value for benign lesions was 1.721×10^{-3} mm^2/sec and the mean ADC value of malignant lesions was 1.075×10^{-3}mm^2/sec respectively. There was a significant difference observed in the mean ADC value of benign and malignant thyroid nodules (p=0.001). Razek AA et al., performed DWI in thyroid nodules and calculated the ADC values. There was a significant difference observed in the mean ADC value of benign lesions (1.8×10^{-3} mm^2/sec) from mean ADC value of malignant lesions (0.73 10^{-3} mm^2/sec) [16]. Erdem G et al., reported using b- values of 0 and 1000 mm^2/sec with mean ADC value of benign lesions as 2.743×10^{-3} mm^2/sec and mean ADC value of malignant lesion as 0.695×10^{-3} mm^2/sec [17]. Wu Y et al., used b-values of 0 and 300 and reported the mean ADC value of benign lesions as 2.37×10^{-3} mm^2/sec, which was significantly higher than that of malignant lesions (1.49×10^{-3} mm^2/sec) [18]. Abd el Aziz LM et al., reported a significant difference in the ADC values of benign and malignant lesions using b-value of 300 mm^2/sec. DWI was done using b-values of 0, 300, 500 and 800 mm^2/sec however, no significant difference was found using b-values of 500 and 800 mm^2/sec [19]. Khizar AT et al., conducted study on 35 patients and calculated the mean ADC value in benign lesions as 1.93×10^{-3} mm^2/sec, which was significantly higher than mean ADC values of malignant lesions as 0.94×10^{-3} mm^2/sec [20]. Wang H et al., conducted a study on a large group of patients with 148 benign thyroid nodules and 111 malignant thyroid nodules and reported that the ADC values in benign lesions (1.95×10^{-3} mm^2/sec) was significantly higher than ADC values in malignant lesions (1.26×10^{-3} mm^2/sec) using b-value of 0 and 800 mm^2/sec [21]. Aghaghazvini L et al., conducted a study using b-values of 50, 500 and 1000 mm^2/sec. The mean ADC value in benign nodules was 1.94±0.54×10^{-3} mm^2/sec and in malignant nodule was 0.89±0.29×10^{-3} mm^2/s with p-value <0.005. Cut-off value of ADC was set to 1×10^{-3} mm^2/s [22]. El-Hariri MA et al., also reported a significant difference between mean ADC of benign (1.85×10^{-3} mm^2/sec) and malignant (0.89×10^{-3} mm^2/sec) thyroid lesions using b-values of 0 and 500 mm^2/sec [23]. There is variation in the cut-off values for the prediction of thyroid carcinomas in different studies and the exact cut-off value should be determined for each MR unit because of variations in the coils, pulse sequences and the MR imaging system [24].

	FNAC-Malignant	FNAC-Benign
DWI-Malignant	15 (a)	3 (b)
DWI-Benign	1 (c)	31 (d)
Sensitivity=a÷(a+c)×100=15/16×100=93.75%		
Specificity=d÷(d+b)×100=31/34×100=91.17%		
PPV= a÷(a+b)×100=15/18×100=83.33%		
NPV=d÷(c+d)×100=31/32=96.87%		
Accuracy=(a+ d)÷(a+b+c+d)×100=46/50=92%		

[Table/Fig-7]: Depicts the sensitivity, specificity, PPV, NPV and the accuracy of the study.

Accurate pre-operative diagnosis of thyroid nodules would improve the surgical planning and reduce unnecessary operation. Therefore, there is a need to inculcate a new non-invasive and reliable radiographic modality that can distinguish between benign and malignant thyroid nodules.

Limitation(s)

Firstly, the study was carried in a small number of cases and needs to be expanded further to a larger population. Secondly, nodules less then 1 cm were not included in the study and improvements in the software of diffusion weighted MR studies will help in detection of smaller lesions in the future.

CONCLUSION(S)

DW-MRI is an easy, non-invasive and rapid technique that does not require i.v contrast administration and can be used for characterising the thyroid nodules. ADC values can be calculated which reliably differentiates benign from malignant thyroid lesions although it does not help to differentiate among the types of malignant thyroid nodules.

REFERENCES

[1] Wong CK, Wheeler MH. Thyroid nodules: Rational management. World J Surg. 2000;24(8):934-41.
[2] Brander A, Viikinkoski P, Nickels J, Kivisaari L. Thyroid gland: US screening in a random adult population. Radiology. 1991;181(3):683-87.
[3] Davies L, Welch HG. Increasing incidence of thyroid cancer in United states 1973-2002. JAMA. 2006;295(18):2164-67.
[4] Nagarkar R, Roy S, Akheel M, Palwe V, Kulkarni N, Pandit P. Incidence of thyroid disorders in India: An institutional retrospective analysis. Int J Dent Med Spec. 2015;2(2):19-23.
[5] Solbiati L, Osti V, Cova L, Tonolini M. Ultrasound of thyroid, parathyroid glands and neck lymph nodes. Eur Radiol. 2001;11(12):2411-24.
[6] Frates MC, Benson CB, Charboneau J, Cibas ES, Clark OH, Coleman BG, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology. 2005;237(3):794-800.
[7] Gritzmann N, Koishwitz D, Retterbacher T. Sonography of thyroid and parathyroid glands. Radiol Clin North Am. 2000;38(5):1131-45.
[8] Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, et al. Risk of malignancy in non-palpable thyroid nodules: Predictive value of ultrasound and colour doppler features. J Clin Endocrinol Metab. 2002;87(5):1941-46.
[9] Pincot SN, Al-Wagih H, Schaerfer S, Cippel R, Chen H. Accuracy of fine needle aspiration biopsy for predicting neoplasm or carcinoma in thyroid nodules 4 cm or larger. Arch Surg. 2009;144(7):649-55.
[10] Huang W, Roche P, Button T, Shindoln M. In vivo 1H MR spectroscopic study of thyroid lesions: Correlation with pathology. Book of abstracts: 10th annual meeting of international society. 2002;10:570.
[11] Uhl M, Altehoefer C, Kontny U, Ilyasov K, Buchert M, Langer M. MRI diffusion imaging of neuroblastomas: First results and correlation to histopathology. Eur Radiol. 2002;12(9):2335-38.
[12] Lyng H, Haraldseth O, Rofstad EK. Measurement of cell density and necrotic fraction in human melanoma xenografts by diffusion weighted magnetic resonance imaging. Magn Reson Med. 2000;43(6):828-36.
[13] Bujang MA, Adnan TH. Requirements of minimal sample size for sensitivity and specificity analysis. JCDR. 2016;10(10):YE01-06.
[14] Ravikanth R, Selvam RP, Pinto DS. Role of quantitative diffusion-weighted magnetic resonance imaging in differentiating benign and malignant thyroid lesions. J Curr Res Sci Med. 2017;3(3):131-33.
[15] Gupta RK, Cloughesy TF, Sinha U, Garakian J, Lazareff J, Rubino G, et al. Relationships between choline magnetic spectroscopy, apparent diffusion coefficient and quantitive histopathology in human glioma. J Neurooncol. 2000;50(3):215-26.
[16] Razek AA, Sadek AG, Kombar OR, Elmahdy TE, Nada N. Role of apparent diffusion co-efficient values in differentiation between malignant and benign solitary thyroid nodules. Am J Neuroradiol. 2008;29 (3):563-68.
[17] Erdem G, Erdem T, Karakas HM, Mutlu DY, Firat AK, Sahin I. Diffusion weighted images differentiate benign from malignant thyroid nodules. J Magn Reson Imaging. 2010;31(1):94-100.
[18] Wu Y, Yue X, Sen W, Du Y, Yuan Y, Tao X, et al. Diagnostic value of diffusion-weighted MR imaging in thyroid disease: Application in differentiating benign from malignant disease. BMC Medical Imaging. 2013;13:23.
[19] Abd el Aziz LM, Hamisa M, Badwy ME. Differentiation of thyroid nodules using diffusion-weighted MRI. Alex J Med. 2015;51(4):305-09.
[20] Khizer AT, Raza S, Slehria AU. Diffusion-weighted MR imaging and ADC mapping in differentiating benign from malignant thyroid nodules. J Coll Physicians Surg Pak. 2015;25(11):785-88.
[21] Wang H, Wei R, Liu W, Chen Y, Song B. Diagnostic efficacy of multiple MRI parameters in differentiating benign vs malignant thyroid nodules. BMC Medical Imaging. 2018;18(1):50.
[22] Aghaghazvini L, Sharifian H, Yazdani M, Hosseeiny M, Kooraki S, Pirouzi P, et al. Differentiation between benign and malignant thyroid nodules using diffusion-weighted imaging, a 3-T MRI study. Indian J Radiol Imaging. 2018;28(4):460-64.
[23] El-Hariri MA, Gouhar GK, Said NS, Riad MM. Role of diffusion-weighted imaging with ADC mapping and in vivo 1H-MR spectroscopy in thyroid nodules. Egypt J Radiol Nucl Med. 2012;43(2):183-92.
[24] Schueller-Weidekamm C, Kaserer K, Schueller G, Scheuba C, Ringl H, Weber M, et al. Can quantitative diffusion-weighted MR imaging differentiate benign and malignant cold thyroid nodules? Initial results in 25 patients. Am J Neuro Radiol. 2009;30(2):417-22.

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