Research Article

Role of Diffusion-Weighted MRI (DWI) in Differentiating Between Benign and Malignant Nodules of Thyroid Taking Histopathology as Gold Standard

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Abstract

Background: Thyroid gland is a principal endocrine organ nodules of which are very common mainly in females with an average prevalence of 34%. Its early diagnosis by a non-invasive imaging investigation that is DWI MRI, help in the diagnosis with high sensitivity and accuracy with greater soft tissue differentiation. The overload of unnecessary surgeries is thus reduced.

Objective: To determine the role of Diffusion-Weighted MRI (DWI) in differentiating between benign and malignant thyroid nodules keeping histopathology as the gold standard.

Methods: One hundred and three patients (103) were enrolled. DWI sequence was performed on 1.5 Tesla GE machine at b-values of 0, 50 and 1000 s/mm^2 with correlative ADC map and quantitative values were calculated. FNAC of the thyroid nodules was carried out and results were tallied with ADC values. Out of these, five patients lost to follow up and an inadequate sample was obtained in six patients.

Results: Mean age of patients (n=92) was 39 years. Out of 92 patients, 26 patients (28.3%) showed restricted diffusion on DWI in malignant thyroid nodules. Mean ADC (Apparent Diffusion Coefficient) value of benign thyroid nodules (1.43×10^{-3}mm^{2}s^{-1}) was significantly greater than malignant thyroid nodules (0.91×10^{-3}mm s^{-1}). For discriminating two types of nodules, cut off ADC value was determined at 1.1×10^{-3}mm^{2}s^{-1} and its sensitivity, specificity, PPV, NPV and diagnostic accuracy was 84.6, 95.4, 88.8, 91.5 and 92.3% respectively.

Conclusion: Diffusion Weighted MRI is a non-invasive imaging investigation without ionizing radiation hazard. Its greater soft tissue differentiation and multiplanar images help in the diagnosis of malignant thyroid nodules with high sensitivity and accuracy. The overload of unnecessary surgeries is thus lowered when pre-operative FNAC is indecisive and aids in making a precise diagnosis.

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Introduction:

Thyroid gland is a principal endocrine organ, first to develop in embryo, endodermal in origin and producing hormones essential for life.[1] It is a vascular organ inclusive of right and left lobes, surrounded by a capsule and isthmus in the centre. Each lobe measures 2cm, 3cm and 5cm in AP, T and CC dimensions[2]. Thyroid nodules are very common mainly in females with an average prevalence of 34%.[3] Clinical examination, neck ultrasound, nuclear scan and fine needle aspiration cytological (FNAC) assessment are the few investigations used for evaluation of the thyroid gland.[4]

However, ultrasound is most commonly used to ascertain thyroid nodules and report them according to Thyroid Imaging Reporting and Data System (TI-RADS) providing information about diameter of nodule, echogenicity, solid or cystic component, width more than length or length more than width, internal comet tail artifacts, calcifications and smooth or ill defined margins. Although there is very less incidence of malignancy, early and authentic diagnosis of malignancy is significant for effective treatment of disease. Furthermore, it is difficult to diagnose the malignant component in large nodules or multi nodular lesions on ultrasound. Recent improvement in MRI may be of increased diagnostic value as it has better image resolution and no involvement of radiation. Dynamic contrast enhancement plays a vital role in diagnosing malignancy as malignant lesions show intense post contrast enhancement while benign lesions do not enhance or show mild post contrast enhancement. Diffusion-weighted imaging (DWI) is an emerging sequence that is sensitive to changes in the microstructure of tissues having water diffusion and is a form of practical imaging that is recently being applied in discrimination of benign from malignant nodules along with Apparent Diffusion Coefficient (ADC) value, a quantitative criterion for this purpose, moreover aiding in staging of tumor and diagnosis of recurrent/ residual disease.[5,6,7] DWI supersedes T1WI post contrast sequence as it is budget friendly, no need to buy contrast and results are more sensitive.

For different b values, ADC maps have to be concluded and compared depending upon cellularity and histopathology. In malignancies, the microscopic pathological changes and high cellularity reduce extracellular space which halts the diffusion of hydrogen molecules, reducing ADC values. Reduced ADC values are retrieved as hyperintense on DWI sequences. Previous studies showed that ADC values were found to be the highest in cystic lesions of thyroid due to benign nature and vary according to the composition of the nodules.[8] Purpose of my study is differentiation of benign from malignant thyroid nodules with a non invasive investigation without the risk of radiation exposure and reduced number of unnecessary surgeries. Although much work has been done on the role of DWI in foreign countries but its accuracy has not been evaluated effectively in our country. This study aims to reduce this knowledge gap and to highlight the importance of DWI in diagnosing malignancy thus planning patient management. Early detection of disease can result in better management of patients with malignancy so that treatment can be started and follow up of patients is assured.

Methods:

An institutional review board approved descriptive cross sectional study was performed in the Radiology Department of Mayo Hospital, Lahore from June, 2019 to May 2021. One hundred and three patients (103) with thyroid nodules assessed by physical examination or neck ultrasound were enrolled in the study. Patients of all ages and both genders referred from the Department of Endocrinology and Surgery were included in the study. Patients with recurrent disease, patients previously taking treatment for thyroid disease, diffuse goiter, patients with pacemakers, prosthetic valves, aneurysm clips, plates, any other ferromagnetic material and claustrophobics were excluded. Sample size (n=103) was calculated by taking sensitivity of 90%, specificity of 95%, absolute precision of 10%, expected prevalence of disease 34% and confidence level of 95%.[9] In all cases histopathological evaluation of the lesions was scheduled. Written informed consent from every patient was taken. Questions were asked regarding age, clinical symptoms, presence or absence of palpable nodules and any previous investigations. All information was recorded in specially designed proforma.

All patients meeting the inclusion criteria underwent MR imaging at 1.5 Tesla GE MRI machine using head coil. Imaging protocol study included axial sequence T2-weighted image with TR of 2400 and TE of 80, matrix size of 310×394, FOV: 220mm and slice thickness = 4 mm) followed by coronal T2-weighted image (TR/TE: 3100/79, matrix size of 310 × 394 FOV: 220 mm, and slice thickness = 5 mm). DWI was acquired in axial sequence on b values of 50, 500 and 1000 with TR of 5500 & TE of 75, slice thickness: 5 mm). After acquiring images, all sequences were seen by using Radiant DICOM viewer. Quantitative ADC values were measured using the software of MRI machine manufacturer. Region of Interest cursor was carefully set in centre of nodule of interest, avoiding cystic and necrotic areas as well as calcifications. Then the ADC value was matched to the type of cytology if it was positive or negative for malignancy. All MRI were reported under the supervision of two qualified radiologists with more than 5 years of post-fellowship experience who were unaware of clinical data of patients. Patients were then sent for FNAC and the slides of all subjects were reported by a qualified pathologist with more than 5 years of post-fellowship experience and reports were obtained. A contingency table was used to calculate sensitivity, specificity, positive predictive value, negative predictive value and accuracy of MRI considering histopathology as the gold standard.

Entry of data and analysis was done by using SPSS version 20. Age was presented as mean. Gender and type of thyroid nodule (on DWI) was presented as frequencies and percentages. Data was stratified for age and type of nodule to overcome confounding. In this study we used uniform sources of information and efficient questionnaire to avoid bias. MRI machine was standardized and checked for artifacts. Sensitivity, specificity, PPV and NPV were calculated by a 2×2 table. The Receiver Operating Characteristic (ROC) curve was drawn to calculate area under the curve.

Results:

During our study, 103 patients were enrolled. Out of these, five patients were lost to follow up and inadequate samples were obtained in six patients. Of these, 53 were females (57.6%) and 39 were male subjects (42.4%). Mean age of patients in the study (n=92) was 39 ± 7.6 years. Twenty five (27.1%) patients had solitary thyroid nodules and sixty seven (72.8%) patients had more than one nodule. Size of the nodules ranged from 1.6 to 5.3 cm with a mean size of 2.8 ± 0.7cm. Results showed that overall 23.9% were true positives, 68.7% were true negatives, 3.3% were false positives and 4.3% were false negatives(Table-1).

Table 1: *Contingency Table n=92*

		Histopathology		Total
		Positive	**Negative**	
DWI (MRI)	Positive for Malignancy	22 (TP)	3 (FP)	25
	Negative for Malignancy	4 (FN)	63 (TN)	67
Total		26	66	92

Results depicted that the sensitivity of ADC value in differentiating benign from malignant thyroid nodules was 84.6%, specificity was 95.4%, positive predictive value (PPV) was 88.8%, negative predictive value (NPV) of 91.5% and accuracy of 92.3% (Table-2).

Involvement of various adjacent structures in individual patients was also seen in our study, some features favoring benign nature of the nodules was size less than 3cm while features which favored malignancy like obvious bone metastasis, tracheo-esophageal groove involvement & cervical lymphadenopathy were also appreciated in this study. Tracheal compression can be seen in both benign and malignant nodules. In sixty one patients (66.3%) size of nodule was less than 3cm. Involvement of isthmus and tracheo-esophageal groove was found in twenty four(26.0%) and nineteen patients(20.6%) respectively. Cervical lymphadenopathy and obvious bone metastasis were seen in eighteen (19.5%) and thirteen subjects (14.1%) respectively. Tracheal compression was present in eleven (11.6%) patients (Table 3).

Table 2: *Summary of Results*

Sensitivity	84.6%
Specificity	95.4%
Positive predictive value	88.8%
Negative predictive value	91.5%
Accuracy	92.3%

Table 3: *MRI findings in Patients of Thyroid Nodules n=92*

Sr #	MRI Findings	Percentage
1	Size of nodule less than 3cm	61(66.3%)
2	Involvement of isthmus	24 (26.0%)
3	Involvement of trachea-eosophageal groove	19(20.6%)
4	Cervical lymphadenopathy	18 (19.5%)
5	Obvious bone metastasis	13 (14.1%)
6	Presence of tracheal compression	11(11.6%)

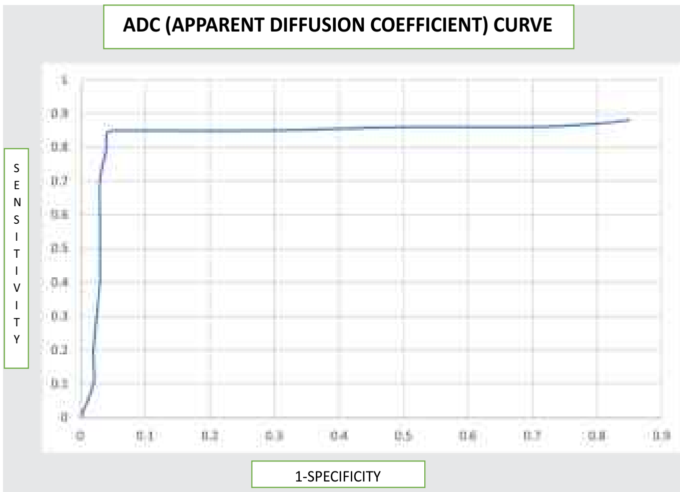
Cytopathology reports were graded as benign including colloid cysts, cases of lymphocytic thyroiditis and multinodular goiter. Malignant lesions included follicular, medullary and papillary carcinomas. In this study, twenty six (28.3%) patients had malignant thyroid nodules and sixty six (71.7%) patients had benign thyroid nodules on cytology. Papillary carcinoma was reported in eleven patients, follicular carcinoma in nine patients whereas medullary carcinoma in six cases. Multi nodular goiter was reported in sixty patients, colloid cyst in three cases and lymphocytic thyroiditis in three cases (Table 4).

Table 4: *Diagnosis of Thyroid Nodules on Cytology n=92*

Cytology	Frequency of Patients
Multinodular Goitre	60 (65.2%)
Papillary Carcinoma	11 (11.9%)
Follicular Carcinoma	9 (9.7%)
Medullary Carcinoma	6 (6.5%)
Colloid Cyst	3 (3.3%)
Lymphocytic Thyroiditis	3 (3.3%)

Mean ADC value of $1.43\times10^{-3}mm^2s^{-1}$ for benign nodules of thyroid was significantly greater than $0.91\times10^{-3}mm^2s^{-1}$ for malignant nodules of thyroid. Cut off ADC value for discriminating the two types of nodules was determined at $1.1\times10^{-3}mm^2s^{-1}$. Area under the ADC curve was calculated which was 0.765. Greater the value of area under the curve, better is DWI as investigation in differentiating between benign and malignant thyroid nodules (Table 5).

Table 5. *ADC Curve and Area under the Curve*



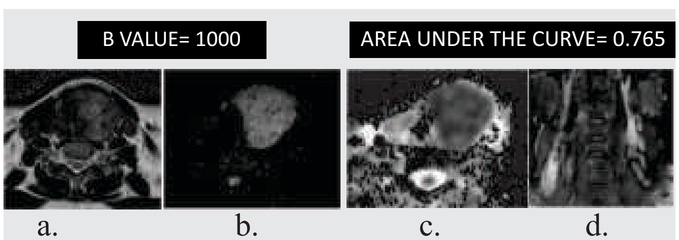


Figure 1: *Images of an indeterminate nodule in the left lobe of thyroid in a young female. Axial T2WI multi echo multiplanar spin-echo at 1.5T showed a heterogenous nodule with hyperintensity in left lobe (a). DWI and its correlative ADC at b value of 1000 (b,c) showed ADC value of* $0.96\times10^{-3}mm^2\,s^{-1}$. *Coronal T2WI shows left cervical lymphadenopathy. Histopathology showed follicular carcinoma.*

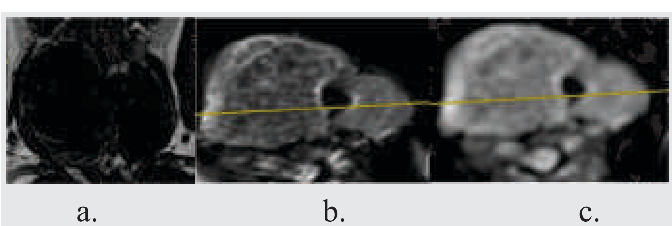


Figure 2: *Images of a neck swelling in an old male which moved on deglutition showed multiple nodules in both lobes of thyroid gland on ultrasound. Coronal T2WI multi echo multiplanar spin-echo at 1.5T showed multiple thyroid nodules, appearing heterogeneously hypointense displacing the trachea towards the left side (a). DWI and correlative ADC at b value of 1000 (b, c) showed ADC value of* $7.96\times10^{-3}mm^2s^{-1}$. *Histopathology showed a multinodular goiter without any malignant nodule.*

Discussion:

Cases of thyroid malignancy have increased dramatically in the last couple of years however thyroid nodules are benign. Less than 5% of nodules are reported to be malignant. 10 year survival rate is high in case of early detection of disease. For detection of calcification and cystic component of nodules, ultrasound shows good diagnostic ability however it is operator dependent. DWI is now a famous radiological investigation and the purpose of the present study was to find the best diagnostic threshold of DWI.[10] We concluded that the ADC values of malignant nodules were considerably lower than benign nodules and these findings were consistent with previous studies.[11]

Neck ultrasound, neck physical examination, scintigraphy and thyroid function tests are the conventional methods for evaluation of thyroid nodules however, these cannot reliably detect malignancy however FNAC is an efficient method.[12] DWI is a sequence for assessing random Brownian motion of water molecules in tissues and is commonly used in routine evaluations. Many studies have reported that the ADC values derived from DWI are used to differentiate the benign and malignant thyroid nodules.[13] The importance of b value is that it affects the quality of image and ADC values. With lower b values, ADC is greater due to perfusion. Maximum b values may be preferred however the inverse relationship between signal-to-noise ratio and b value restricts maximum b value.[14] ADC value was not very helpful due to difference in its values according to the composition of nodule including colloid material, necrotic and cystic component, fibrosis, calcification and hemorrhage. In this study, ADC values were maximum in thyroid cysts as it contained serous material (colloid fluid). Low ADC value in thyroid cancer were due to increased cellularity and fibrous connective tissue.[15]

Production of an image with better contrast and spatial resolution is the aim of all radiological investigations [16].

A study was conducted by Nofal and Shailage in 2017 which concluded that the sensitivity and specificity of DWI for differentiating benign from malignant nodules was 85.7 and 89.2 respectively using ADC value of $1.5\times10^{-3}mm^2s^{-1}$ [17]. Hao Wang et al conducted a study of 181 patients which showed that ADC value, tumor diameter, cystic component, hyperintense area on T1-weighted imaging and irregular shape showed prominent variances between the two groups of patients. ADC is the best in differentiating between benign and malignant nodules. Abd- Alhamid T, Khafagy AG et al conducted a study on 49 patients which showed 63.3% benign nodules showing lower ADC values and 36.7% malignant cases with high ADC values.[18]

Yoshifumi Noda et al. performed a study on thirty six patients which included ten male and twenty six female with an age range of 14–79 years(mean age was 57.7 ± 15.5 years). The patients had solid nodules in the thyroid gland, diagnosed by ultrasonography and then MRI was done on patients before FNAC or thyroidectomy. Statistic analysis showed that ADC value of 1.88 ± 0.5 for the benign thyroid nodules was remarkably greater ($p < 0.0001$) as compared to malignant lesions (0.89 ± 0.1).[19] A study conducted by Khizer AT et al. concluded that ADC value of $905 \times 10^{-6}/mm^2s^{-1}$ was the cut off value for differentiation with 90% sensitivity and specificity of 100%.[20]

Relatively small number of malignant nodules limiting the statistical power, exclusion of small thyroid nodules less than 10 mm, susceptibility of DWI to some artifacts like distortions, T2 blackout, motion artifact, T2 shine through and ghost artifact were some of the limitations in this study. Tissues with very long relaxation times are hyperintense on DWI at high b value as well as ADC, defined as T2 shine through which is in contrary to restricted diffusion, which shows low signal on ADC maps. The strengths of our study were that we included patients of different age groups, histopathology of the thyroid nodules was done and we followed up with the patients for better results. Some limitations were that our sample size was small and few patients were also lost to follow-up which might have resulted in selection bias.

In the present study, sensitivity was found to be 84.6%, specificity was 95.4%, positive predictive value (PPV) was 88.8%, negative predictive value (NPV) was 91.5% and accuracy of dynamic contrast MRI in detecting thyroid malignancy was 92.3%.

Conclusion:

MRI DWI is a reliable, budget friendly and non-invasive imaging modality that helps in the diagnosis of thyroid malignancy with high specificity, sensitivity and accuracy superseding contrast enhanced sequence which is costly in terms of buying contrast material. Our study concluded that a cut off ADC value of $1.1\times10^{-3}mm^2s^{-1}$ was used for discriminating between the two types of nodules and percentages of different cytological types. We also concluded that the involvement of adjacent structures including isthmus and tracheo- esophageal groove, tracheal compression, bone metastasis and cervical lymphadenopathy was only possible with MRI.

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Conflict of Interest: The authors declare no conflict of interest.
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