Research Article

Differentiation between benign and malignant thyroid nodules by diffusion weighted image and apparent diffusion coefficient

Mohammad T. M. Soliman*, Mohammad H. Alam-Aldeen*,
Tarek E. Fotohy and Gehad A. Mohammad Ead***
* Department of Diagnostic Radiology, Faculty of Medicine, Sohag University
** Department of Maxillofasical, Head and Neck Surgery, Faculty of Medicine, Sohag University

Abstract

Background: There is a great increase in the incidence of thyroid cancer. Thyroid cancer is the most common endocrine tumor. Magnetic resonance imaging (MRI) has gained importance in the diagnosis of thyroid cancer. The application of diffusion-weighted MRI (DWI) is an important diagnostic tool for assessing in vivo tumor characterization. **Objective:** The purpose of the study is to evaluate the diagnostic accuracy of diffusion weighted imaging and ADC to differentiate between benign and malignant thyroid nodules. **Methodology:** this investigation has been done through assortment of information from papers which has been looked upon PubMed, the papers have been from 1998 to 2o16, the hunt is finished including just the papers written in English language and assortment of the information including radiological anatomy of thyroid gland ,hint about the physics of MRI, DWI and ADC as well as appearance of different thyroid lesions at DWI and ADC**.** **Conclusion:** DWI with the ADC values may be a doable, non-invasive and non-radiative technique for recognizing malignant from benign thyroid nodules that do not require the administration of contrast media. The b value is a significant factor, and different b-values must be acquired for more accurate quantitative analysis of diffusion-weighted images and consequently reliable ADC maps as well as the ADC measurement.

Keywords: Malignant thyroid nodules, DWI, ADC

Introduction

There is a great increase in the incidence of thyroid cancer. Thyroid cancer is the most common endocrine tumor.Thyroid ultrasonography can provide information with regard to nodule diameter, structure of the nodule whether cystic or solid, presence of calcification, regular margin and absence of halo sign but still no reliable criteria for distinguishing benign from malignant lesions. In addition, it is difficult to diagnose the malignancy of the nodule when it is large or multinodular[1]**.**

Diagnostic imaging examinations such as radionuclide scintigraphy and sonography are commonly used to attempt differentiation between benign and malignant thyroid nodules. However, these modalities have many limitations, such as poor accuracy with sonography and exposure to ionizing radiation with nuclear scintigraphy[2].

The differentiation of single benign nodule and malignant one is considered an important goal. Early diagnosis of thyroid cancer avoids unneeded surgery in those complaining of benign nodules and decreases both mortality and morbidity rates of the disease[3].

Several studies have evaluated the characteristics of sonography as a potential predictor of thyroid malignancy. Although there are certain sonographic features characteristic for the distinction of benign and malignant thyroid nodules, there is also an overlap in the appearance of these features. Because of the low predictive value of sonographic features, the cyto-pathologic evaluation of a thyroid nodule is usually required before surgical resection is scheduled. So ultrasound-guided fine-needle aspiration (USgFNA) is the method of choice for the evaluation of a thyroid lesion on a cytologic level[4].

Recent developments in MRI may show that some MR protocols are of diagnostic value for these types of lesions. Routine T1- and T2-weighted MR imaging can provide information on the location and size of thyroid lesions. But these protocols still don't have the specificity for distinguishing benign from malignant nodules or assessing the functional status of these thyroid nodules[6]. DWI is sensitive to changes in the microstructural organization of tissue that may affect water diffusion. It has been used to evaluate head and neck tumors. The Apparent Diffusion Coefficient (ADC) value is a quantitative parameter for distinguishing malignant tumors from benign thyroid nodules[1].

Magnetic resonance imaging (MRI) has gained importance in the diagnosis of thyroid cancer. The application of diffusion-weighted MRI (DWI) is an important diagnostic tool for assessing in vivo tumor characterization. Several studies have shown that DWI has the potential to differentiate benign from malignant nodules in the thyroid. Structural changes of malignancies or benign thyroid tissue can be evaluated with the apparent diffusion coefficient (ADC), which is an objective parameter of the tissue-specific diffusion capacity of a biologic tissue[4].

Aim of the Work

The purpose of the study is to evaluate the diagnostic accuracy of diffusion weighted imaging and ADC to differentiate between benign and malignant thyroid nodules.

Thyroid nodules

Thyroid nodules are nodules (raised areas of tissue or fluid) which commonly arise within an otherwise normal thyroid gland. They may be hyperplasia or a thyroid neoplasm, but only a small percentage of the latter are thyroid cancers. Small, asymptomatic nodules are common, and many people who have them are unaware of them. But nodules that grow larger or produce symptoms may eventually need medical care. Goitres may have nodules or be diffuse[7].

Thyroid nodule genesis may be considered as an amplification of thyroid heterogeneity due to genetic and/or epigenetic mechanisms. We classified the thyroid nodules in five types with distinct histological features: hyperplastic, neoplastic, colloid, cystic and thyroiditic nodules[7].

Diagnosis:

After a nodule is found during a physical examination, a referral to an endocrinologist, a thyroidologist or otolaryngologist may occur. Most commonly an ultrasound is performed to confirm the presence of a nodule, and assess the status of the whole gland. Measurement of thyroid stimulating hormone and anti-thyroid antibodies will help decide if there is a functional thyroid disease such as Hashimoto's thyroiditis present, a known cause of a benign nodular goitre. Fine needle biopsy for histopathology is also used[8].

Thyroid nodules are extremely common in young adults and children. Almost 50% of people have had one, but they are usually only detected by a physician during the course of a health examination or fortuitously discovered during the investigation of an unrelated condition[8].

Ultrasound:

Figure (1): Comet tail artifacts from a colloid nodule is highly suggestive of a benign nodule[9].

Ultrasound imaging is useful as the first-line, non-invasive investigation in determining the size, texture, position, and vascularity of a nodule, accessing lymph nodes metastasis in the neck, and for guiding fine needle aspiration cytology (FNAC) or biopsy. High frequency transducer (7–12 MHz) is used to scan the thyroid nodule, while taking cross-sectional and longitudinal sections during scan. Suspicious findings in a nodule are hypoechoic, ill-defined margins, absence of peripheral halo or irregular margin, fine, punctate microcalcifications, high levels of irregular blood flow within the nodule or "taller-than-wide sign" (anterior-posterior diameter is greater than transverse diameter of a nodule)[9].

Fine-needle aspiration biopsy:

FNAB has emerged as the most important step in the diagnostic evaluation of thyroid nodules. Data from numerous studies have established FNAB as highly accurate, with mean sensitivity higher than 80% and mean specificity higher than 90%. The accuracy of FNAB in diagnosing thyroid conditions highly depends on the cytopathologist's expertise and experience and the technical skill of the physician performing the biopsy. In addition, FNAB is highly cost-effective compared with traditional workups that heavily depended on nuclear imaging and ultrasonography. Routine use of FNAB in the evaluation of thyroid nodules can reduce the need for diagnostic thyroidectomy by 20-50% while increasing the yield of cancer diagnoses in thyroid specimens by 15-45%[1o].

Basic Physics of DW Imaging:

DW imaging is an MR technique that depicts molecular diffusion, which is the brownian motion of water protons in biologic tissues. Examination of molecular diffusion by using MR imaging relies on sensitizing an imaging sequence with two equally strong but opposed gradients along a certain diffusion direction. While the first of these two diffusion-sensitizing gradients induces dephasing, the second will completely rephase all stationary molecules. Movement in living tissues, however, results in incomplete rephasing, which is translated into a signal intensity decrease on the resulting image. The signal intensity decrease is dependent on the amount of moving molecules, their respective speed along the diffusion-sensitizing gradient, and the strength of the diffusion- sensitizing gradients[11].

Diffusion-weighted magnetic resonance imaging (**DWI** or **DW-MRI**) is the use of specific MRI sequences as well as software that generates images from the resulting data, that uses the diffusion of water molecules to generate contrast in MR images. It allows the mapping of the diffusion process of molecules, mainly water, in biological tissues, in vivo and non-invasively. Molecular diffusion in tissues is not free, but reflects interactions with many obstacles, such as macromolecules, fibers, and membranes. Water molecule diffusion patterns can therefore reveal microscopic details about tissue architecture, either normal or in a diseased state[12].

In **diffusion weighted imaging** (DWI), the intensity of each image element (voxel) reflects the best estimate of the rate of water diffusion at that location. Because the mobility of water is driven by thermal agitation and highly dependent on its cellular environment, the hypothesis behind DWI is that findings may indicate (early) pathologic change. For instance, DWI is more sensitive to early changes after a stroke than more traditional MRI measurements such as T1 or T2 relaxation rates. A variant of diffusion weighted imaging,

Diffusion spectrum imaging (DSI), was used in deriving the Connectome data sets; DSI is a variant of diffusion-weighted imaging that is sensitive to intra-voxel heterogeneities in diffusion directions caused by crossing fiber tracts and thus allows more accurate mapping of axonal trajectories than other diffusion imaging approaches[12].

Diffusion-weighted images are very useful to diagnose vascular strokes in the brain. It is also used more and more in the staging of non-small-cell lung cancer, where it is a serious candidate to replace positron emission tomography as the 'gold standard' for this type of disease. Diffusion tensor imaging is being developed for studying the diseases of the white matter of the brain as well as for studies of other body tissues. DWI is most applicable when the tissue of interest is dominated by isotropic water movement e.g. grey matter in the cerebral cortex and major brain nuclei, or in the body—where the diffusion rate appears to be the same when measured along any axis. However, DWI also remains sensitive to T1 and T2 relaxation. To entangle diffusion and relaxation effects on image contrast, one may obtain quantitative images of the diffusion coefficient, or more exactly the apparent diffusion coefficient (ADC). The ADC concept was introduced to take into account the fact that the diffusion process is complex in biological tissues and reflects several different mechanisms[13].

Choice of b Values:

The diffusion-sensitizing effect from the gradients is indicated by the p value (in seconds per square millimeter), which is defined by the gradient strength, the duration of the gradients, and the time interval between the gradients[14]. Whereas fast-moving molecules will quickly lose all of their phase coherence and signal intensity, even at low p values, slow-moving molecules will retain high signal intensities far into the higher ranges of p values. By examining the remaining signal intensity on DW images obtained with different p values, the amount and speed of movement can be estimated and quantified by using the so-called apparent diffusion coefficient (ADC, expressed in square millimeters per second), which is calculated by means of a least-squares fit of the signal intensities from images ac-quired with different p values, with either a mono-exponential or a biexponential diffusion model.

The p values used in DW imaging are, therefore, very important. However, the selection of p values is not always straight forward. The largest p value used in the sequence defines the timing and the echo time of the sequence, and a longer echo time yields markedly reduced signal-to-noise ratio on the resulting images. Therefore the highest b value should be chosen carefully and should not be too high, because images obtained with lower b values in the same sequence will be acquired by using the same echo time, resulting in lower signal-to-noise–ratio images than might be optimal. Currently, most clinical studies are performed with a maximum b value of 1000 sec/mm2[15].

Image Analysis:

A prerequisite for performing DW MR imaging in the head and neck is to acquire adequate morphologic images—if possible with the same field of view, section thickness, and orientation—to provide overlay images and correctly interpret anatomic localization, as well as observe morphologic findings. There is no consensus on the minimum size of head and neck lesions that can be reliably detected. The recommendation in a recently published consensus article on DW imaging of cancer is a minimum lesion size of 2 cm for accurate ADC calculation[16].

Qualitative analysis.—Qualitative evaluation is performed by means of visual assessment of the signal intensity on images acquired at high b values and their corresponding ADC maps. A solid tumor shows high signal intensity on a high-b-value image and low signal intensity on the corresponding ADC map, whereas apoptosis or necrosis commonly appear as areas of low signal intensity on high-b-value images with high signal intensity on corresponding ADC maps[17].

Quantitative analysis.—Next to visual assessment of lesions in the head and neck, the most common method of analysis uses quantification through the calculation of ADC. As with tumors in other locations, no standard method has been established to determine the ADC for commonly encountered head and neck tumors. Simple methods of acquiring a mean ADC include the drawing of multiple small regions of interest on one or several sections or a single large region of interest on one section or calculation of ADC from the entire lesion[17].

ADC image:

An apparent diffusion coefficient (ADC) image or an ADC map is an MRI image that more specifically shows diffusion than conventional DWI, by eliminating the T2 weighing that is otherwise inherent in conventional DWI. ADC imaging does so by acquiring multiple conventional DWI images with different amounts of DWI weighing, and the change in signal is proportional to the rate of diffusion. Contrary to DWI images, the standard grayscale of ADC images is to represent a smaller magnitude of diffusion as darker [15].

Diffusion-weighted MR imaging and apparent diffusion coefficient (ADC) in diagnosis of thyroid nodules:

A thyroid nodule is a discrete lesion within the thyroid gland that is distinguishable from the adjacent parenchyma. A study by sonography of a population group older than 50 years showed that 50% had thyroid nodules. In enlarged nodular thyroids, sonographic examination demonstrated that two thirds had multiple nodules, whereas one third had single nodules. Among these nodules, 85%–90% were proved to be benign[18].

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[19]. Tezuka et al.,[20] in their study using diffusion-weighted MR imaging to assess the thyroid function, reported that the ADC values of patients with Grave's disease exceeded those of patients with subacute thyroiditis, with a sensitivity and specificity of 75% and 80%, respectively, in differentiating between both disease entities. They concluded that diffusion-weighted MR imaging could be clinically important in evaluating the thyroid function. Diffusion-weighted MR imaging can provide better characterization of the tissues and their physiologic processes because it reflects the random motion of water protons, which is disturbed by intracellular organelles and macromolecules located in the tissues. Thus, the ADC values of the tissues vary according to the physiologic state of the tissue[21]. Diffusion-weighted MR imaging has been used for differentiation between benign and malignant head and neck masses, characterization of the cervical lymph nodes, and discrimination of recurrent or residual tumors from post treatment changes in the head and neck[22].

Furthermore, mean ADC values were significantly different between FTC, PTC and undifferentiated thyroid carcinoma, whereas the ADC maximum values resulted positively correlated with some histopathological indexes, i.e. cell count and total nuclei area, in a clinical series of 20 patients. Nonetheless, the correlation between ADC with Ki-67 index and p53 expression, which are a marker of cell proliferation and a tumor suppressor, respectively, did not reach statistical significance[22]. Anderson[23] reported that malignant tumors have enlarged nuclei and hyperchromatism. These histopathologic characteristics reduce the extracellular dimension that results in a decrease in the ADCs of malignant lymph nodes. Preliminary studies that used diffusion-weighted MR imaging in the head and neck have shown good correlation between the ADC values and the histopathologic nature of the tumors. Wang et al.,[22] reported that the differences in histopathologic features of both benign and malignant head and neck tumors explain the differences in their ADC values. They added that malignant tumors have increased cellularity compared with benign masses, with subsequent decrease of the ADC values. There is a relatively wide range of ADC values in adenomatous nodules (1.1:1.9) x10^{-3} mm2/s and follicular adenomas (1.2–2) x10^{-3} mm2/s. This may be explained by the relative abundance of the different components forming these nodules (colloid, microcystic necrosis, hemorrhage, fibrous tissue, and calcification). The contributions of these different components may alter the ADC value and explain the variability of the ADC value found among patients with benign nodules[22].

Abdel Razek et al.,[24] found that a thyroid cyst has the highest ADC value because it may contain serous fluid or may be a colloid cyst with high thyroglobulin concentration. one patient had a hemorrhagic cyst that was misdiagnosed as a malignant tumor with a low ADC value. The cause of this decrease in ADC value was the presence of hemorrhage within the cyst with subsequent restricted diffusion and a low ADC value. There were significant differences between cystic and solid thyroid nodules (adenomatous nodules and follicular adenomas), with P = 0.001. The cystic or hemorrhagic thyroid nodule did not benefit from diffusion weighted MR imaging. The FNAB helped in characterization of the nature of the fluid within the thyroid cysts. Also they reported that malignant tumors of the thyroid gland showed low ADC values compared with benign nodules, but there were insignificant differences in the mean ADC values of the various malignant nodules, with P = .464. Abundant hyperplastic nuclei in malignant tumors and calcified psam- moma bodies in papillary thyroid carcinoma are responsible for low ADC values. Most thyroid cancers are papillary cancer (75%:80%), whereas the remainning histologic types will consist of approximately 10%:20% follicular, 3%:5% medullary, and 1%:2% anaplastic cancer. ADC measurements can also be used in the differentiation of benign and malignant thyroid nodules and in the literature a few articles were found about this topic even though they gave controversial results[25].

Another study performed by Bozgeyik et al., [26] included 88 benign and 5 malignant thyroid nodules. They used b factors of 100, 200 and 300 s / mm² for ADC measurements. The mean ADC values of malignant and benign nodules were 00.96 ± 0.65 x1o^{-3}mm² /s and 3.06±0.71 x1o^{-3}mm² / s for b-100 factor, 0.56 ± 0.43 x10^{-3}mm² / s and 1.80 ± 0.60 x10^{-3}mm² / s for b-200 factor, and 0.30± 0.20 x10^{-3} mm² / s and 1.15 ± 0.43x10^{-3}mm² /s for b-300 factor, respectively. They concluded that benign thyroid nodules present with higher ADC values than malignant nodules and DWI may be helpful in this differentiation[26].

Abdel Razek et al.,[27] study demonstrated that when selecting ADC value of 0.98 x10^{-3}mm2/s as a cutoff point to differentiate benign and malignant lesions, the sensitivity and specificity was 97.5% and 91.7%, respectively. The accuracy was up to 98.9%. In their study a single pair of p values (0, 1000 s/mm2) were studied. Although they also looked at the ADC values obtained using higher b-values (0,800 s/mm2), they did not detect any useful threshold at the higher p-values. Abdel’s study included a variety of cervical lymph nodes. Lesion heterogeneity might have accounted for the differences in sensitivity. It was also suggested that the ADC values of benign thyroid nodule may vary according to the complex composition within the nodule (colloid, tiny necrosis and cystic change, hemorrhage, fibrosis and calcium). ADC values were highest in thyroid cysts since it contained colloid cyst made of serous or concentrated thyroglobulin. Conversely, increasing NCR and grit-like calcification mainly lead to a decrease of ADC values in papillary thyroid carcinoma[27].

The ADC values depend on many factors such as tissue microstructure, necrosis, presence of macromolecules and perfusion phenomenon. When compared to benign lesions, abnormal blood perfusion is more prevalent in malignant lesions and ADC values will be affected by both blood perfusion and extracellular space[28].

Delorme and Knopp[29] demonstrated that malignant lesions usually do not have a complete basal membrane of blood vessel, which enhances the molecular exchange in the capillary bed. ADC values could be influenced by both blood perfusion and extracellular space. In thyroid malignancy, increased blood perfusion increases the apparent speed of the diffusing water protons while narrow extracellular space will restrict its movement. Although at higher b-values the sensitivity to perfusion is reduced, their results show no difference in ADC values between benign and malignant groups with b-values of 500 s/mm2 or 800 s/mm2. The ADC values obtained using the lower b-value of 3oo s/mm2 is most likely affected by both perfusion and diffusion effects. It is possible that the discriminatory effect of this lower 300 s/mm2 reflect a combination of altered vascularity and changes in cellular composition that characterizes malignancy[29].

on the other hand Schueller-Weidekamm et al.,[4], used b value 800 in their study on cold thyroid nodules found lowADC values for adenomas (1.93 x 10^{-3} mm2/s) and high ADC values in thyroiditis and thyroid carcinomas (P2.73 x10^{-3} mm2/s). Their explanation was that thyroid carcinoma cannot be compared with other malignancies in the body as the cellular components depend on the macrofollicular production of thyreoglobulin, which results in an unrestricted diffusion capacity. In addition, the presence of microcalcifications influences the DWI and signal intensities.

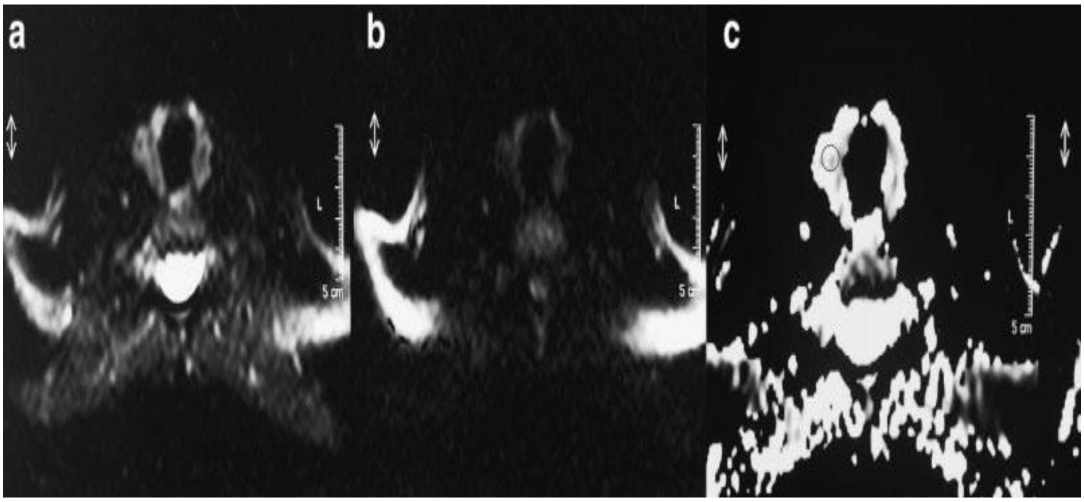

Figure (2): A 32-year-Old woman with normal hyroid gland. Axial T2-weighted (a), DW image (b), and ADC map (c). The ADC value measured as 1.24 x10^{-3} mm2/s[29].

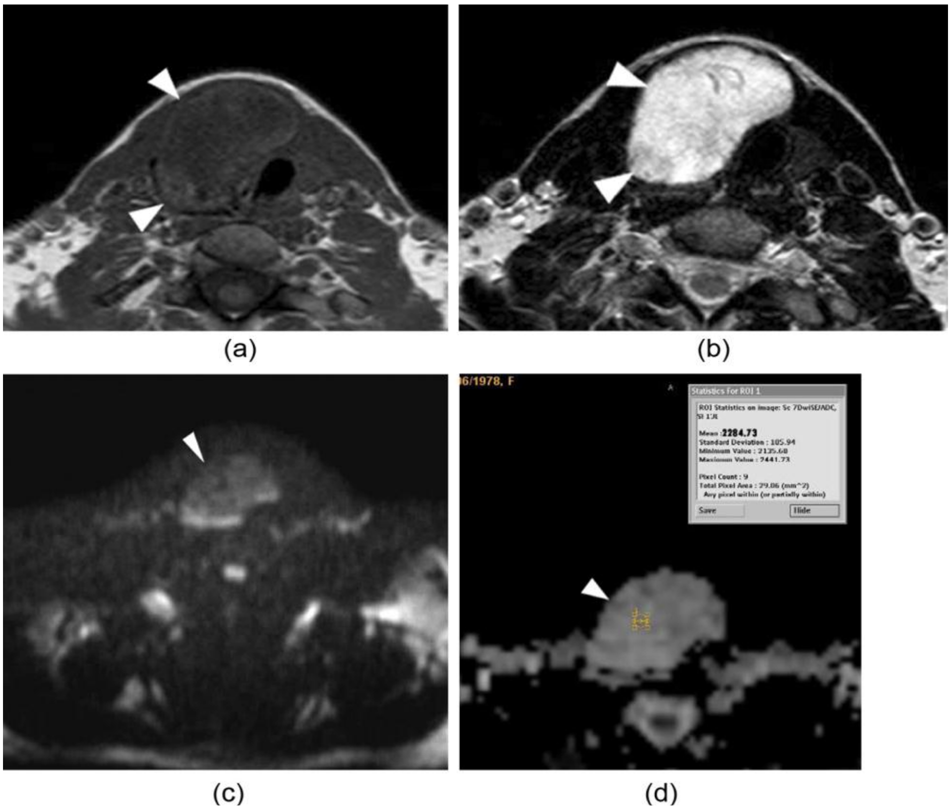

Figure (3): (a) Axial T1WI shows a well defined hypointense lesion in the right lobe of thyroid gland. (b) Axial T2 WI shows well defined hyperintense lesion. (c and d) Axial D image and ADC map image with p-value of 1000 s/mm2 show low and high signal intensity respectively of the lesion denoting free diffusion. ADC value (p = 500) is 2.49 x10^{-3} mm2/s. ADC value (p = 1000) is 2.28 x10^{-3}mm2/s. The lesion has DWI readings suggestive of benign lesion[3].

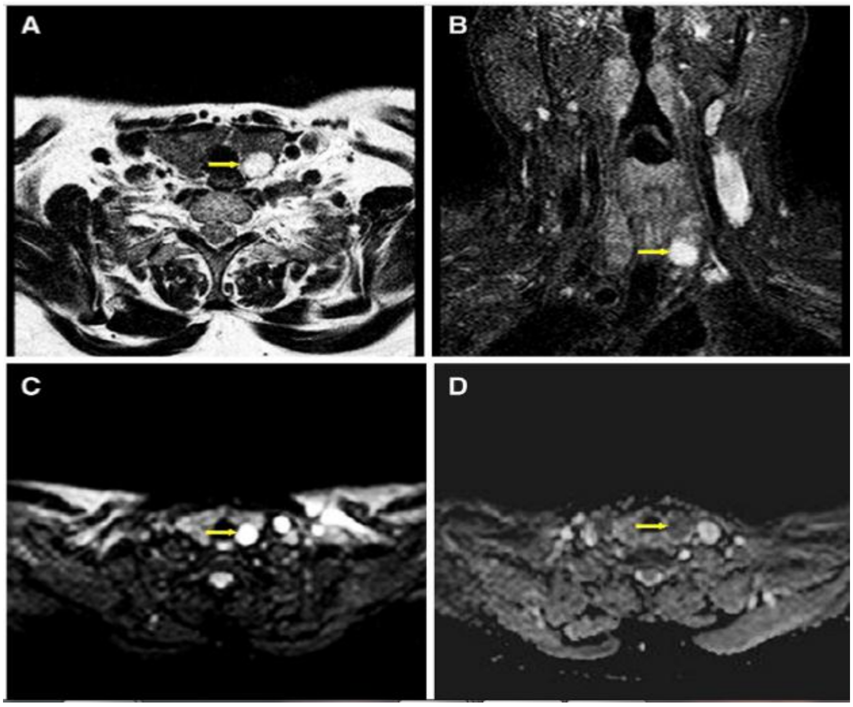

Figure (4): (A–D) Thyroid follicular carcinoma. Axial T2-weighted (A) and coronal STIR (B) MR images show a well-defined hyperintense nodule in the left thyroid lobe (yellow arrows). Increased diffusion and relative hypointensity are shown in the axial DWI (C) and ADC map image (D) with a measured ADC value of 0.816±0.21 x10^{-3} mm2\s (yellow arrows)[30].

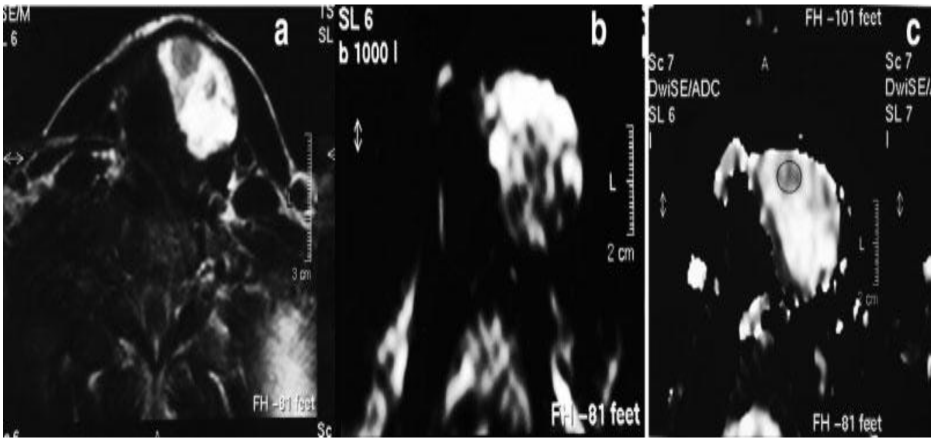

Figure (5): A 32-year-old woman with a malignant nodule in left thyroid lobe (papillary thyroid carcinoma). Axial T2-weighted (a), DW image (b), and ADC map (c). ADC map reveals low signal intensity in solid areas. Solid nodular area designed with a circle has an ADC value of 1.07 mm2/s x10^{-3} [2].

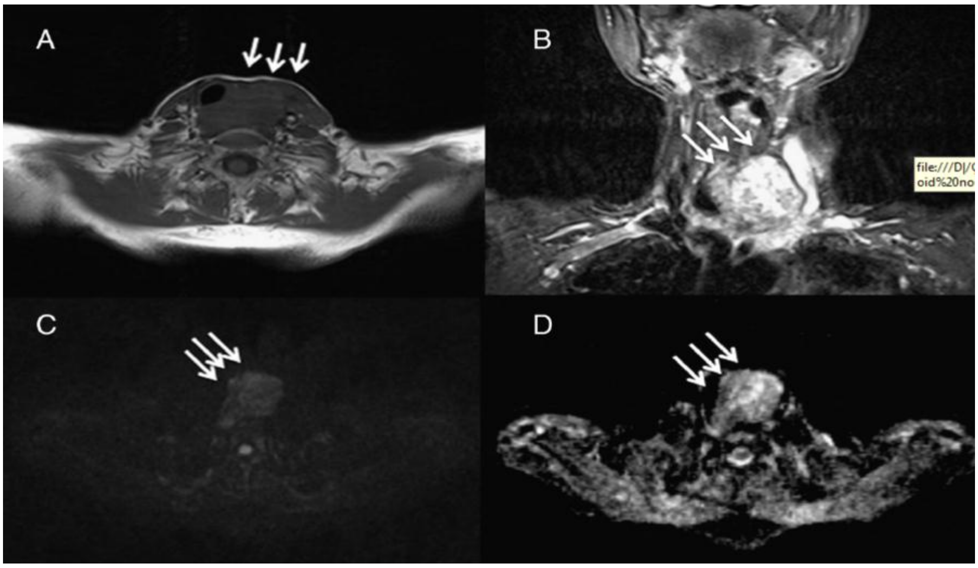

Figure (6): (A) A 5o-year-old female patient with complaints of hoarseness and having enlarged thyroid glands, rightward trachea deviation, and obstruction on left jugular vein on T1 weighted images. (B) A heterogeneous mass lesion having lobular contour on coronal T2 images causes tracheal pressure. (C) Mass lesion is hyperintense on DWimages. (D) MeanADC values are measured 1.1× $x10^{-3}$mm2/s on ADC map. FNAB of the nodule was diagnosed as medullary thyroid cancer[5].

Conclusion

In conclusion, DWI with the ADC values may be feasible, non-invasive and non-radiative method of distinguishing malignant from benign thyroid nodules that do not require the administration of contrast media. The b value is a very important factor, and different b-values have to be acquired for more accurate quantitative analysis of diffusion-weighted images and consequently reliable ADC maps as well as the ADC measurement.

ADC values of nodules may provide useful data about the nature of a thyroid nodule with significant difference in the ADC value between benign and malignant thyroid lesions, which ADC values in benign lesions being higher than malignant lesions.

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