

Role of Diffusion Weighted Magnetic Resonance Imaging in Characterization of Pulmonary Masses

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Abstract

Background: Lung malignancy is the most common cause of death in the developed countries. Male to female ratio is 3:1. Consumption of Tobacco upsurges the rate of evolving lung cancer by 30 folds. Other risk factors include repeated exposure to aspects like carcinogens, asbestos, pulmonary fibrosis and radiotherapy.

Aim of Study: The aim of this study is to assess the role of diffusion weighted magnetic resonance imaging in characterization of pulmonary masses.

Patients and Methods: This study was carried out on forty (40) patients 8 females and 32 males who had Pulmonary mass on the X-ray or CT chest and aged above 18 years old. All the studied patients underwent to detailed history taking, laboratory studies and radiological examination using MRI (GE 1.5 Tesla) using body phased-array Coil and DWI (b-value 0, 500, and 800s/mm²).

Results: Thirty lesions were malignant, and 10 lesions were benign. The malignant masses showed significantly higher signal intensity on DWI than benign masses ($p < 0.001$), and the mean ADC value of malignant lesions was significantly lower than that of benign lesions ($p < 0.001$). By ROC curve, an ADC cut-off value of $1.6 \times 10^{-3} \text{ mm}^2/\text{s}$ was considered the threshold value, and the sensitivity and specificity were 100% and 90% respectively.

Conclusion: Diffusion-weighted MRI and ADC can significantly differentiate between benign and malignant pulmonary masses.

Key Words: Diffusion MRI – ADC – Benign – Malignant – Pulmonary lesions.

Introduction

IMAGING plays a critical role in detection and characterization of pulmonary masses if benign or

malignant because the therapy depends on the nature of the mass, a lung mass requires careful differential diagnosis to choose the optimal treatment for each patient [1].

Computed Tomography (CT) and Positron Emission Tomography (PET) are two common non-invasive methods used to examine pulmonary nodules or masses with high diagnostic accuracy, but these two methods have increased radiation exposure and the sensitivity of PET-CT is low in nodules smaller than 20mm, so another non-invasive method is required in the differential diagnosis of lung masses to avoid unnecessary biopsies that cause many risks and complications [2].

MRI is a powerful tool for research and specific clinical applications, although Computed Tomography (CT) remains the gold standard for imaging of lung patho-morphology in cancer patients. The advantages of MRI over CT are not only limited to the lack of ionizing radiation but also combines excellent soft tissue contrast and functional information, it allows for multiple and repeated measurements and can be used to assess motion and perfusion of thoracic organs [3].

In addition to T1 and T2 weighted imaging, many MR techniques have been designed to extract metabolic or biophysical information. Diffusion Weighted MR Imaging (DWI) is a non-invasive technique that is capable of probing the structure of biological tissues at a molecular level by the random and motion of water molecules in biological tissues and can be quantified by the Apparent Diffusion Coefficient (ADC), which refers to the

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specific diffusion capacity of a biological tissue [4].

ADC relates to the molecular transitional movement of water molecules. Decrease ADC values correlates with increased tumor cellularity which tends to restrict water diffusion [5].

The ability to measure the rate of water diffusion within tissue is important, as water diffusion is altered in various disease processes and can reflect physiological and morphological characteristics such as cell density and tissue viability [6].

DWI of body organs has become possible with fast imaging times but motion-related artifacts such as respiration and cardiac movement decrease image quality and limited its clinical application for evaluation of pulmonary diseases [7].

Patients and Methods

This study was carried out on (40) patients who were referred from Clinical Oncology and Nuclear Medicine Department to the Radiodiagnosis and Medical Imaging Department Faculty of Medicine, Tanta University Hospitals in the period from October 2017 to December 2018.

Inclusion criteria:

- 1- Patients aged above 18 years old.
- 2- Pulmonary mass on the X-ray or CT chest.

Exclusion criteria:

- 1- Contraindications to MRI including cardiac pacemaker, ferromagnetic haemostatic clips in CNS, claustrophobia and patients with prosthetic valve.
- 2- Patients who were having bleeding disorders so were insuitable for taking biopsy.

Ethical consideration:

The final learning protocol that was received and approved by the Medical Research Committee of the Faculty of Medicine and the managers of the hospitals in which the study will be conducted. Further, every patient who was to take part in the study was informed over the activity in advance. Important to note, the exercise was voluntary, none of the individuals was forced in one way or the other to participate in the tests. To sum up, personal concealment was respected in all stages of the study. Any data collected from the participants will not be used for any other purpose other than the one it's intended for.

Clinical assessment:

By history taking, patients are either symptomless or symptomatic like dyspnea, chest pain, hemoptysis, and cough. And for general symptoms like fever, weight loss and hoarseness of voice.

Radiological examination:

Twenty patients have pulmonary lesions in their chest radiograph and the others have pulmonary masses in their CT chest.

MRI technique:

All MRI studies were conducted with (GE 1.5 Tesla), using body phased-array Coil, all the patients were in a supine position all over the checkup. Several axial & coronal scans of the chest were obtained. The MR scanning sequences were T1WI, T2WI, DWI and ADC map.

T1 fast spin echo weighted images were obtained with the following parameters: Repetition time 470ms, echo time 13ms, matrix 270 X 220, field of view 76, slice thickness 7mm, gap 1mm, flip angle 70°.

Respiratory gated T2-weighted fast spin echo images were obtained using the following parameters: Repetition time 1250ms, echo time 70ms, matrix 325 X 280 field of view 89, Slice thickness 7mm, gap 1 mm.

DWI: The distribution gradient was applied in the three orthogonal directions (X, Y, Z). From the tests, diffusion-weighted MRI was acquired with b factor of 0, 500, 800. With the following parameters: Repetition time 2020ms, echo time 70ms, matrix 168 X 168, field of view 85, slice thickness 5mm, gap 6mm, flip angle 90°.

ADC maps were automatically calculated by the software on the basis of the pictures obtained. ADC was worked out by drawing elongated Regions of Interest (ROI) with a regular size of 5-25 voxels. All the ROIs were located in the most restricted area of the lesion.

Assessment of diffusion weighted image:

Each lesion was evaluated for its size, extent, and relation to adjacent structures. Its signal intensity was evaluated in all pulse sequences T1WI, T2WI and its signal in DWI and ADC map were compared.

ADC values were calculated from the ADC charts which were created from b=0 and b=800 sec/mm² values. Similarly, ROI was drawn centrally

and were kept significantly large on the ADC chart avoiding macroscopic necrosis and main blood vessel. The average of three measurements was finally recorded as the final findings.

Pathological diagnosis:

Histo-pathological analysis was our standard reference. Tissues used for histo-pathological examination for final diagnosis were undertaken by: Fine needle aspiration, true cut biopsy or by surgical excision.

Results

Our study included 40 patients with pulmonary masses; eight were benign and 32 were malignant. The benign lesions included 6 males and 4 females, with mean age 46.8 ± 7.8 years, age range 36-55 years. The malignant lesions included 26 males and 4 females, with mean age $49.2 \pm .6$ years, age range 26-65 years.

The benign group (n=10), 4 of them were smokers (40%) and 6 (60%) were non-smokers, while the malignant group (n=30) 28 (93.3%) of them were smokers and 2 (6.6%) were non-smokers. The final diagnosis of the lesions was confirmed by histopathological examination either by fine needle aspiration, true cut biopsy or by surgical excision. The final pathological diagnosis was adenocarcinoma 10 patients (25%), squamous cell carcinoma 6 cases (15%), small cell carcinoma 6 cases (15%), large cell carcinoma 4 cases (10%), metastatic 4 cases (10%), lung abscess 4 cases (10%), hydatid cyst 3 cases (7.5%), cavernous hemangioma 2 cases (5%), and Fibrous tumor 1 case (2.5%) (Table 1).

There was statistically significance difference between smoking and the development of benign and malignant masses (p -value <0.001) (Table 2).

In case of lung cancer, the highest ADC value was that of adenocarcinoma ($1.440 \pm 0.107 \times 10^{-3}$ mm/s) and the lowest ADC value was that of large cell carcinomas ($0.750 \pm 0.300 \times 10^{-3}$ mm/s).

In benign lesions, the highest ADC value was that of cavernous hemangioma ($2.750 \pm 0.354 \times 10^{-3}$ mm/s), and the lowest ADC value was that of pyogenic abscess ($1,825 \pm 0.299 \times 10^{-3}$ mm/s).

There was statistically significant difference when comparing different pathological lesions with the mean ADC value (p -value >0.001) (Table 3).

When comparing the mean ADC value of NSCLC and SCLC showed that ADC value of SCLC was lower than that of NSCLC ($1.12 \pm 0.45 \times 10^{-3}$ vs. $0.80 \pm 0.12 \times 10^{-3}$) with no significance difference (p -value=0.106) (Table 4).

The malignant lesions tend to show high signal on DWI (restricted diffusion pattern) while benign lesions tend to show low signal on DWI (free diffusion pattern) comparing to the signal of adjacent muscles.

Three patients had non-restricted diffusion pattern, 2 of them were malignant and were proven to be squamous cell carcinoma. One case proved to be fibroma and it was benign. Thirty two cases had restricted diffusion pattern, 4 of them were benign, and proved to be pyogenic abscess. And 28 cases were proved to be malignant.

Five cases showed free diffusion pattern and all were benign lesions. There was statistically significance difference when comparing signal intensity of DWI with nature of pulmonary masses (p -value >0.001) (Table 5).

Table (1): Pathological diagnosis of pulmonary masses included in the study.

	N	% pathology	% total
Adenocarcinoma	10	33.33	25.00
Squamous cell carcinoma	6	20.00	15.00
Large cell carcinoma	4	13.33	10.00
Small cell carcinoma	6	20.00	15.00
Metastatic	4	13.33	10.00
Pyogenic abscess	4	40.00	10.00
Hydatid cyst	3	30.00	7.50
Cavernous hemangioma	2	20.00	5.00
Fibroma	1	10.00	2.50
Total	40	100.00	100.00

Table (2): Relation between smoking and nature of pulmonary masses.

Smoking	Nature of pulmonary mass						Chi-Square	
	Benign		Malignant		Total		χ^2	p-value
	N	%	N	%	N	%		
No	6	60.00	2	6.67	8	20.00	13.333	<0.001*
Yes	4	40.00	28	93.33	32	80.00		
Total	10	100.00	30	100.00	40	100.00		

Table (3): Comparison between different histopathological lesions and the mean ADC value.

	ADC value (X 10 ⁻³)		t-test or ANOVA	
	N	Mean ± SD	t or F	p-value
<i>Histopathology:</i>				
Adenocarcinoma	10	1.440±0.107	10.179	<0.001 *
Squamous cell carcinoma	6	0.833±0.547		
Small cell carcinoma	6	0.800±0.126		
Large cell carcinoma	4	0.750±0.300		
Pyogenic abscess	4	1.825±0.299		
Hydatid cyst	3	2.067±0.208		
Metastatic	4	1.000±0.577		
Cavernous heamangioma	2	2.750±0.354		
Fibroma	1	2.500±0.000		

Table (4): Mean ADC value of NSCLC and SCLC.

	ADC value (X 10 ⁻³)		t-test	
	N	Mean ± SD	t	p-value
<i>Non-Small Cell Lung Cancer (NSCLC):</i>				
• Adenocarcinoma, large cell carcinoma, squamous cell carcinoma)	20	1.120±0.455	1.681	0.106
Small cell lung cancer (SCLC)	6	0.800±0.126		

Table (5): DWI of pulmonary masses included in the study.

SI of DWI	Nature of pulmonary mass					Chi-Square		
	Benign		Malignant		Total		χ^2	p-value
	N	%	N	%	N	%		
Non restricted	1	10.00	2	6.67	3	7.5	22.333	<0.001 *
Restricted	4	40.00	28	93.33	32	80.00		
Free	5	50.00	0	0.00	5	12.5		
Total	10	100.00	30	100.00	40	100.00		

The mean ADC value of benign lesions was (1.9±0.284 X 10⁻³ mm²/s), and for malignant lesions it was (1.04±0.435 X 10⁻³ mm²/s) which was significantly lower than the benign lesions with (p-value <0.001) (Table 6), Fig. (1).

Table (6): The mean ADC value of benign and malignant lesions.

ADC value (X10 ⁻³)	Nature of pulmonary mass		t-test	
	Benign	Malignant	t	p-value
Range	1.5-2.4	0.3-1.6	6.161	<0.001 *
Mean ± SD	1.950±0.284	1.040±0.435		

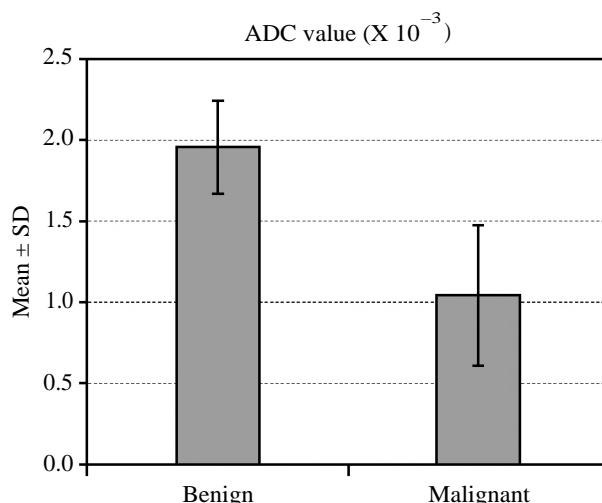


Fig. (1): Mean ADC value of benign and malignant lesions.

The area under the ROC (Receiving Operator Characteristic) Curve was 0.98. A cut off value (1.6 X 10⁻³ mm²/s) was considered to be the threshold. When an ADC value of 1.6 X 10⁻³ mm²/s or more, the lesion was considered to be benign and a value below the threshold was considered to be malignant, the sensitivity was (100%) and specificity was (90%), positive predictive value (96.8%) and negative predictive value (100%) (Table 7), Fig. (2).

Table (7): Receiver Operating characteristic Curve and ADC value of pulmonary masses.

ROC curve between malignant and benign					
Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
≤1.6	100.0	90.0	96.8	100.0	98.3 %

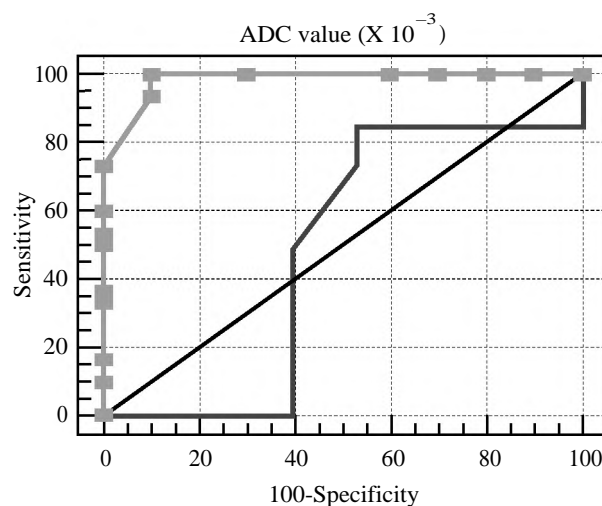


Fig. (2): Receiver Operating Characteristic (ROC) curve of ADC value in benign and malignant pulmonary masses (n=40).

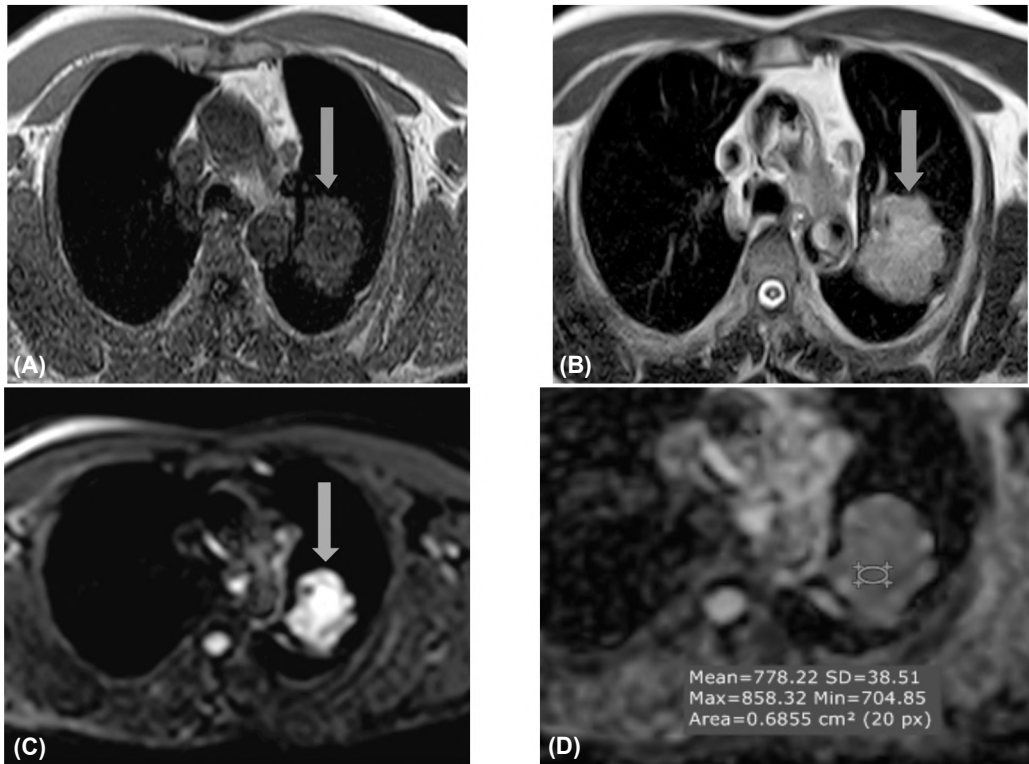


Fig. (3): Male patient 50 years old presented by dyspnea and cough. Pathological diagnosis: Small Cell Lung Carcinoma (SCLC). (A) Axial T1-WI showing well defined mass at the RT lung with low signal intensity. (B) Axial T2-WI showing high signal intensity of the mass. (C,D) Axial DWI showing restricted diffusion pattern of the lesion. The ADC map showing the mean ADC value $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$.

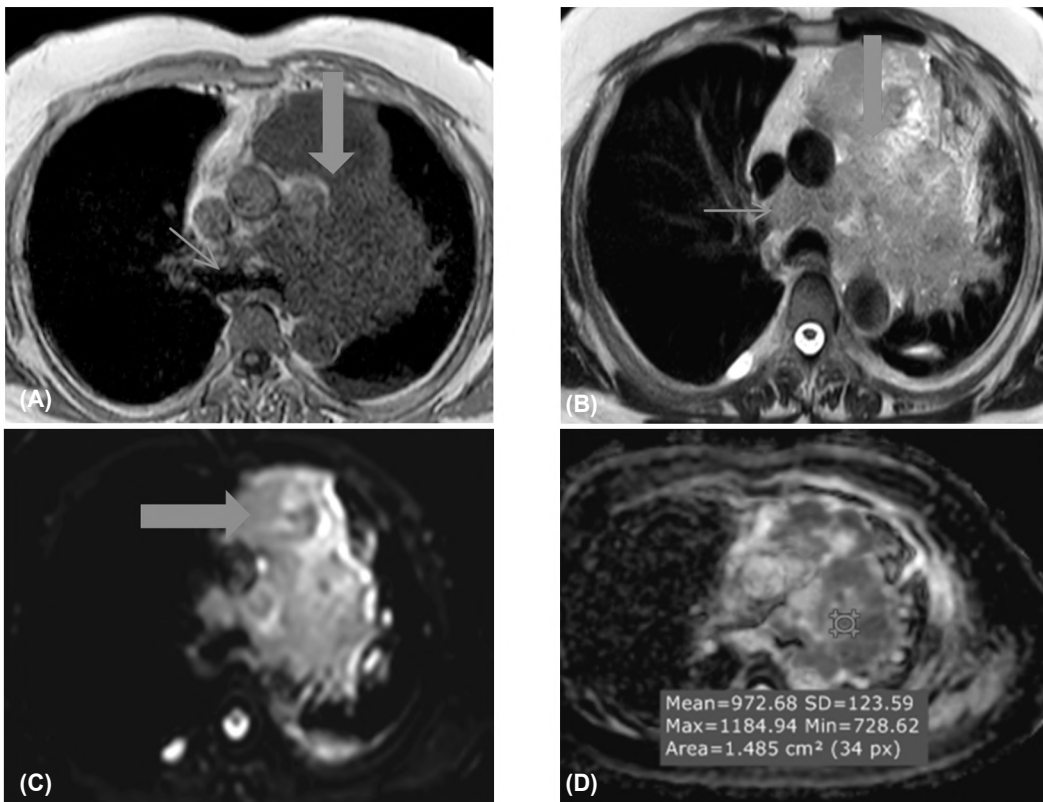


Fig. (4): Male patient 50 years old presented by dyspnea and cough. Pathological diagnosis: NSCLC (Squamous cell carcinoma). (A) Axial T1-WI showing a large irregular shaped mass with low SI in left lung seen encasing the pulmonary artery with enlarged mediastinal LN (thin red arrow). (B) Axial T2-WI showing high SI of the lesion and LN. (C,D) Axial DWI showing restricted diffusion. ADC map showing mean ADC value $0.9 \times 10^{-3} \text{ mm}^2/\text{s}$.

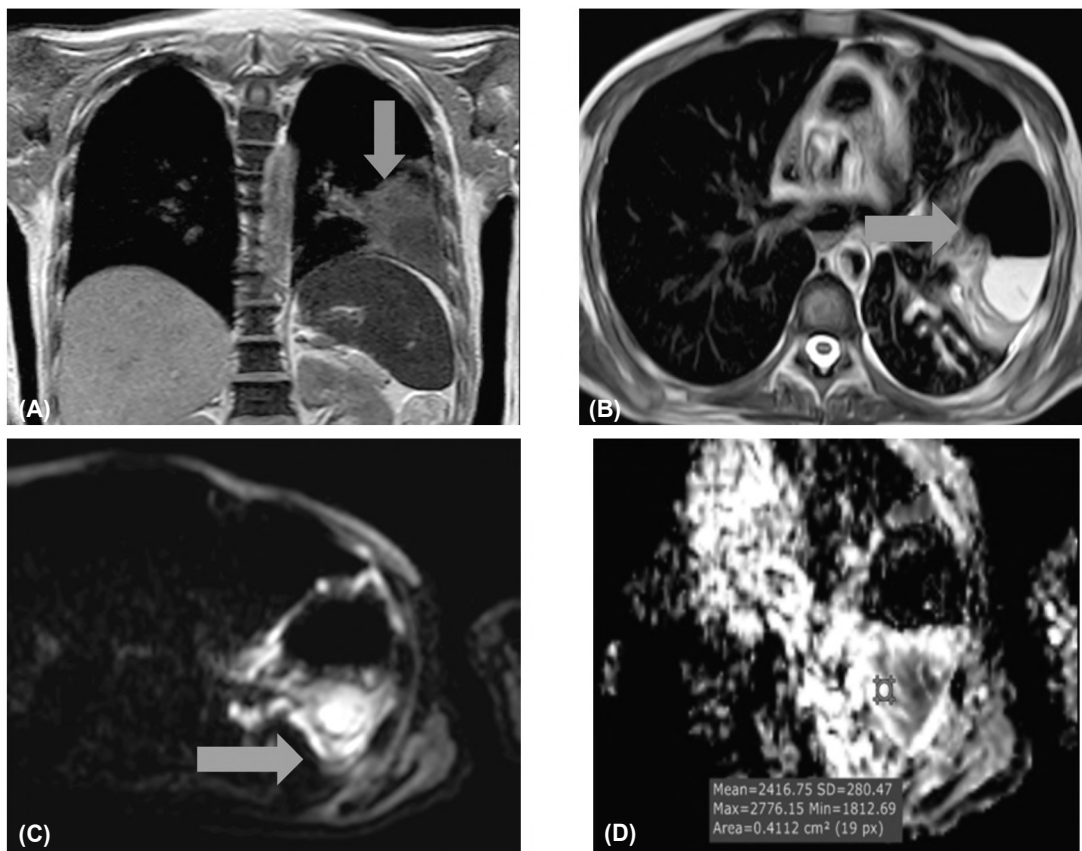


Fig. (5): Forty five years old male presented by fever and weight loss. Pathological diagnosis: Lung abscess (A) Coronal T1WI showing large ill-defined lesion at the LT lower lung lobe with low signal intensity (B) Axial T2WI, the cavity shows air fluid level with hyper-intense signal of the fluid inside (C,D) Axial DWI showing restricted diffusion pattern of the fluid inside the cavity. ADC map showing mean ADC value $2.4 \times 10^{-3} \text{ mm}^2/\text{s}$.

Discussion

Diffusion weighted MRI detects the random motion of water molecules in the biological tissues, this is called "Brownian motion" and helps in characterization of tissue microstructural changes. Water diffusion is changed in various disease processes reflecting physiological and morphological tissue criteria such as cell density and tissue viability. This can be quantified by Apparent Diffusion Coefficient (ADC) value [8].

The clinical application of pulmonary (MRI) was limited due to physical motion artifacts and technical limitations. However, with the development of technology in recent years, MRI has become a clinically feasible method for specific pulmonary problems [9].

Our study included 40 patients with pulmonary masses, including 10 benign lesions and 30 malignant lesions.

In this study, there was strong relation between developing lung cancer and smoking (p -value

<0.001). Thirty-two patients were smokers, 28 patients showed different malignant lung masses. This result was in agreement with (Danson et al., 2016) [10].

In our study the malignant lesions showed high signal on DWI with restricted diffusion pattern, and some benign lesions showed low signal on DWI with free diffusion pattern in agreement with the results obtained by Liu et al., [4].

However, we had four benign lesions with restricted diffusion pattern; they proved to be lung abscesses. This restricted pattern was due to the high viscous content inside the swollen abscess cavity. Normally, water particles move freely in the extracellular partition. In the pyogenic abscess, the movement of the particles is largely distressed by elements like macro-organisms, protein, and inflammatory cells. Important to note, all the components in the abscess are large in size and the ADC value is inversely proportional to the value of the proteins. However, the cause of the hyper-intense appearance on the DWI is due to the re-

striction of the spontaneous microscopic movement of water particles by the bacteria, inflammatory cells, cellular debris, and protein complex. This limits the haphazard motion of the particles leading to diffusion restriction resulting in high signal [11]. Four cases had non-restricted diffusion pattern 3 proved to be malignant and one proved to be benign; so we cannot depend on visual assessment only to judge the nature of a lesion, whether benign or malignant.

The associations between ADC value and histopathological parameters were analyzed in 30 malignant and 10 benign lesions, with statistically significance ($p < 0.001$), this was in agreement with (Zhang et al., 2018) [12] by working out the ADC value, a lot of studies and researches showed that ADC values of various malignant lesions upsetting various organs in the body like the hepatic, renal, prostatic and uterine tumours were lower than those of benign lesions or normal tissues and showed high signal intensity (restricted pattern) on the DWI [4]. Therefore, the ADC values were anticipated to reflect the histopathological tissue features by a non-invasive technique, not demanding for ionizing radiation [4].

ADC values: Our study demonstrated that the mean ADC value of benign lesions was $1.9 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$ and for malignant lesions it was $1.04 \pm 0.4 \times 10^{-3} \text{ mm}^2/\text{s}$, which was significantly lower than that of the benign lesions. This result was in agreement with the results of Liu et al., [4], (Gumustas et al., 2011) [13] and (Nasr et al., 2016) [14].

The area under the ROC curve was 0.98, and a cut-off value $1.6 \times 10^{-3} \text{ mm}^2/\text{s}$ was considered to be the threshold; the sensitivity and specificity were 100% and 90%, respectively. In different results; (Abdel Razek et al., 2009) [15] reported cut off ADC value ($1.56 \times 10^{-3} \text{ mm}^2/\text{s}$) with sensitivity and specificity 96% and 94% respectively, and (Gumustas et al., 2011) [13] reported cutoff ADC value ($1.39 \times 10^{-3} \text{ mm}^2/\text{s}$) with sensitivity and specificity of 95% and 87% respectively. Liu et al., 2010 [4] reported different cut off values of the ADC ($1.4 \times 10^{-3} \text{ mm}^2/\text{s}$).

Histopathologically, tumor cellularity of SCLC is high, and these tumor cells have very large nuclei and almost no cytoplasm. These features were expected to restrict the tissue diffusion and reduce ADC values. SCLC is differentiated from other forms of lung cancer by its aggressive clinical course, widespread metastasis and its sensitivity to chemotherapy and radiation therapy. Treatment

for SCLC and NSCLC are not the same. Surgery is the treatment of choice for patient with NSCLC while chemotherapy and radiotherapy is the standard for SCLC. So; it is important and of clinical significance to distinguish between both types [116].

Although ADCs were lower in the SCLC than in NSCLC subgroup, the difference was not statistically significant (p -value=0.106). This may be because of the limited number of patients ($n=6$). This was in agreement with (Cakmak et al., 2016) [16] who found that there was no significance between ADC values of SCLC & NSCLC. However, this was not in agreement with the results of (Abdel Razek et al., 2012) [17] as they found that there were significantly lower ADC values for SCLC when comparing with NSCLC groups in a similar patient population. Liu et al., 2010 [4] also found that the ADC values for the SCLC were significantly lower than the NSCLC group (p -value=0.007).

Our study had many limitations, first, difficulty to avoid artifacts, breathing movement and cardiac motion which cause image distortion and difficult interpretation of DWI especially in small sized lesions that may be missed with breathing or motion.

Second, there were a small number of patients in the benign group. This may be due to the fact that the admitted patients only have malignant lesions and need further evaluation and treatment. Also not all benign pulmonary lesions went through histological validation and we included only the pathologically confirmed cases.

Third, the distribution of malignant tumors was not homogeneous.

Fourth, we placed small ROIs on the solid portions of pulmonary lesions, avoiding the areas of necrosis, hemorrhage, and artifacts. ROI that covers all tumor volumes would minimize the inter observer variability and ensure repeatable and reproducible ADC measurement. However, inclusion of intra tumoral hemorrhagic, cystic, or necrotic areas may adversely affect ADC values due to extremes in water ADC values.

Conclusions:

Diffusion MR imaging offers functional imaging of lung cancer due to its ability to probe the microstructure of the tumors, which is complementary to the routine anatomic MR imaging of the chest. The potential value of diffusion MR imaging is in its detection and characterization of lung cancer.

It can be obtained in a short time without injection of contrast medium. The gradual development and standardization of imaging sequences and widespread research will make diffusion MR imaging of the chest more suitable for clinical applications in the future.

ADC values can be used to differentiate between benign and malignant pulmonary masses. Diffusion-weighted MRI and measurements of ADC value are very helpful in evaluating pulmonary masses and can differentiate between benign and malignant lesion, so it can reduce unnecessary biopsy and thoracic surgery for non-neoplastic benign lesions.

Conflict of interest:

The authors report no conflict of interest.

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دور الفحص بالرنين المغناطيسي باستخدام خاصية الانتشار في تقييم الكتل الرئوية

مقدمة: لقد أثبت فحص الرنين المغناطيسي بالانتشار أنه وسيلة حديثة في التفرقة بين الكتل الخبيثة والكتل الحميدة الموجودة بالرئة. فهو يعتمد على الحركة الانتشارية للماء في الأنسجة، والأمراض التي تصيب الأنسجة تؤدي إلى تغير في الحركة الطبيعية للمياه وبالتالي تغير في قيمة معامل الانتشار الظاهري.

في فحص الرنين المغناطيسي بالانتشار تتميز الأورام الخبيثة بإشارة عالية بالإضافة إلى إنخفاض في قيمة معامل الانتشار الظاهري بينما تتميز الكتل الحميدة بإنخفاض قوة الإشارة وزيادة قيمة معامل الانتشار الظاهري.

الغرض من البحث: تقييم دور فحص الرنين المغناطيسي باستخدام خاصية الانتشار في التفرقة بين كتل الرئة الحميدة والخبيثة.

المرضى: تمت الدراسة بقسم الأشعة التشخيصية بمستشفيات جامعة طنطا على عدد أربعين (٤٠) مريض.

معايير التضمين:

١- وجود كتل بالرئة في أشخاص لا تقل أعمارهم عن ١٨ سنة.

٢- أن لا يقل حجم الكتلة المراد تشخيصها عن إثنان ونصف سنتيمتر.

معايير الإستبعاد: وجود أى موانع لعمل فحص الرنين المغناطيسي مثل: جهاز تنظيم ضربات القلب أو المشبك العلاجي في حالات تمدد الأوعية الدموية بالمخ.

طريقة البحث: تم الفحص باستخدام جهاز رنين مغناطيسي ١.٥ تسلا لتقييم الكتل المراد تشخيصها وتم التصوير باستخدام خاصية الانتشار للتمييز بين الكتل الحميدة والخبيثة وكذلك قياس قيمة معامل الانتشار في جميع الحالات. تم أخذ عينات من جميع الكتل وتم فحصها وتشخيصها باثولوجيا ومقارنتها بنتائج الرنين المغناطيسي وتم إستخراج المعيار المرجعي الحساسية والنوعية (١٠٠٪ و ٩٠٪) للكتل الموجودة بالرئة.

الإستنتاج: أظهرت نتائج هذه الدراسة أن فحص الرنين المغناطيسي باستخدام خاصية الانتشار لتقييم كتل الرئة يعتبر أداة سريعة وغير تداخلية ودقيقة خاصة في التفرقة بين الكتل المختلفة الحميد منها والخبيث حيث أنه يعتمد على التغير في قيمة معامل الانتشار الظاهري التي تختلف طبقاً لإختلاف نوع النسيج الذي تم فحصه: ففي حالة الكتل الحميدة تزيد قيمة معامل الانتشار الظاهري بينما تقل تلك القيمة في حالة الكتل الخبيثة مما يؤدي إلى سهولة التفرقة بين الكتل المختلفة وتقليل التدخل الجراحي الغير ضروري لأخذ عينه من أجل تشخيص الحالة.