

Dynamic Contrast - Enhanced Magnetic Resonance Imaging (DCE-MRI) in Diagnosis of Pulmonary Nodules

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Abstract

Background: The differentiation between the benign and malignant pulmonary nodules has been considered as a major challenge for many years. Despite the fact that biopsy and histopathological evaluation are crucial for the definitive diagnosis, recent non-invasive imaging modalities are promising in their results.

Aim of Study: The aim of this study is to evaluate the role of Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) in diagnosis of pulmonary nodules.

Patients and Methods: This study is a cross-sectional study that has been conducted on 60 patients with lung nodules referred to Radio Diagnosis and Imaging Department from Chest and Oncology Departments through the period from September 2018 to September 2019.

Results: There were statistically significant differences between malignant and benign cases in terms of maximum net enhancement ($p=0.003$) and ADC value ($p<0.001$). The mean maximum net enhancement was 474 ± 94.417 , the mean washout ratio was $5.45 \pm 2.17\%$, and the mean ADC value was $1.2 \pm 0.34 \times 10^{-3} \text{ mm}^2/\text{sec}$. Malignant cases had significantly higher maximum net enhancement, washout ratio, and lower ADC values. The maximum enhancement curve was a significant discriminator, which yielded a sensitivity of 92.6% and specificity of 96% at a cut-off value of ≥ 375 . In contrary, the ADC value had poor diagnostic accuracy in differentiating between malignant and benign cases.

Conclusion: Dynamic contrast-enhanced MRI is valuable for diagnosis of pulmonary nodules and discrimination of benign from malignant ones.

Key Words: *Magnetic Resonance Imaging – Pulmonary nodules – Dynamic contrast enhanced.*

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Introduction

THE evaluation of pulmonary nodules is one of the most frequently encountered challenges in thoracic radiology [1].

The study of tumor neo angiogenesis is currently a leading theme in oncology. It has become challenging goal for radiologists to non-invasively assess the physiology of the tumor microcirculation and its conventional morphology [2].

Angiogenesis is now extensively studied by Dynamic Contrast Enhanced (DCE) magnetic resonance imaging. Recent clinical studies have shown that DCE-MRI can assess tumor aggressiveness and measure tumor response to therapy [3].

Dynamic MRI has higher soft tissue contrast than CT and is useful for assessing tumor vascularity, interstitium, and vascular endothelial growth

List of Abbreviations:

CT	: Computed Tomography.
MRI	: Magnetic Resonance Imaging.
DCE-MRI	: Dynamic Contrast Enhanced Magnetic Resonance Imaging.
PET/CT	: Positron Emission Tomography combined with Computed Tomography.
DWI	: Diffusion Weighted Imaging.
ADC	: Apparent Diffusion Coefficient.
SI	: Signal Intensity.
WFSE	: Weighted Fast Spin Echo.
NLST	: National Lung Screening Trial.
SPSS	: Statistical Package for the Social Sciences.
Mmol	: Millimole.
Msec	: Millisecond.
IQR	: Interquartile Range.
SD	: Standard Deviation.
PPV	: Positive Predictive Value.
NPV	: Negative Predictive Value.
AUC	: Area Under Curve.
CI	: Confidence Interval.

factor expression. These advantages make dynamic Magnetic Resonance Imaging (MRI) an ideal method for characterizing tumor response to anti-angiogenic treatment as well as for predicting survival outcomes after treatment, in addition to non exposure to radiation [4].

Dynamic contrast enhanced imaging describes the acquisition of a base line images without contrast enhancement followed by a series of images acquired over time after intravenous bolus of contrast agent [5].

Dynamic contrast enhanced MRI is helpful in differentiating benign and malignant pulmonary nodules. Absence of significant enhancement is strong predictor that the lesion is benign [6,7].

The aim of this study is to evaluate the role of Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) in diagnosis of pulmonary nodules.

Patients and Methods

This study is a cross-sectional study that has been conducted on 60 patients with lung nodules referred to Radio Diagnosis and Imaging Department from Chest and Oncology Departments through the period from September 2018 to September 2019. Patients with contrast media allergy or with metal implants were excluded. The patients presented with dyspnea and hemoptysis with different primary malignancies.

MR imaging was performed with a 1.5T MR scanner (Magnetom Expert; Siemens, Erlangen, Germany) by using the phased-array coil as the receiver. For lesion detection, the chest was examined from the apex to the base by using a transverse breath-hold ECG gated proton-density-weighted gradient-echo MR sequence (repetition time msec/echo time msec, 800-1,000/6 ; flip angle, 20°; voxel size, 1.3 X 1.3 X 6.0mm).

Dynamic contrast-enhanced MR images were acquired in the sagittal plane every 10 seconds over a total period of 4 minutes by using a T 1 WI in phase gradient-echo MR sequence (20/4.8; flip angle 70°; voxel size 1.4 X 1.4 X 8.0mm). Although expiratory breath holds are considered more reproducible, the images were acquired in inspiration because we assumed a better delineation of the lesion against enhanced vessels and inflated lung parenchyma.

Rapid bolus injection of a standard dose of 0.1 mmol/kg of gadopentetate dimeglumine (Magnev-

ist; Schering, Berlin, Germany) followed by 20mL of 0.9% saline was started at the time of acquisition of the second image (of a series of 24 images). All MR imaging examinations were completed within 25 minutes.

Mean SIs of the lesions were measured on the operator console by a chest radiologist with 5 years of experience, who placed a freehand ROI (region of interest) that encompassed all of the cross-sectional visible area of the lesion. Visible pulmonary vessels beneath the lesion were excluded from the region of interest. All measurements were obtained without prior knowledge of the histologic diagnosis. SI of the nodules was determined for each time point (t), and time-intensity curves were plotted automatically for every lesion Fig. (1).

The following parameters were evaluated:

- 1- Early Peak (EP) was determined as the highest SI value in the first 30 seconds.
- 2- Maximum Peak (MP) represented the maximum SI value during the entire observation time.
- 3- First transit slope represented the mean velocity SI increase per second from the beginning of the examination to the time of Early Peak (EP) enhancement.
- 4- Washout phase was used to assess the changes in SI per second for the 60-second time interval after the early peak.
- 5- Mean enhancement represented the mean value of all measurements of SI.

Single shot echo planar spin echo Diffusion Weighted Imaging (DWI) was performed with two b factors (0 and 1000s/mm²). Apparent Diffusion Coefficients (ADCs) were also calculated.

Two radiologists experienced in chest radiology performed a retrospective morphologic analysis of contrast enhancement by means of consensus. Images of the time series were displayed in cine mode on the operator console. Medians and interquartile ranges were calculated for the parameters of the time-intensity curves and the nodule diameters Fig. (1). Five enhancement patterns were distinguishable: No enhancement, homogeneous enhancement, heterogeneous enhancement, nodular enhancement and marginal enhancement.

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors.

The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPs Inc, Chicago, IL, USA). Frequency tables with percentages were used for categorical variables and descriptive statistics. Median and Interquartile Range (IQR) were used for numerical variables. Independent student *t*-test, paired *t*-test, or Mann-Whitney tests were used to compare quantitative variables, while Chi-square test or McNemar-Bowker tests were used to analyze categorical variables. A *p*-value <0.05 is considered statistically significant.

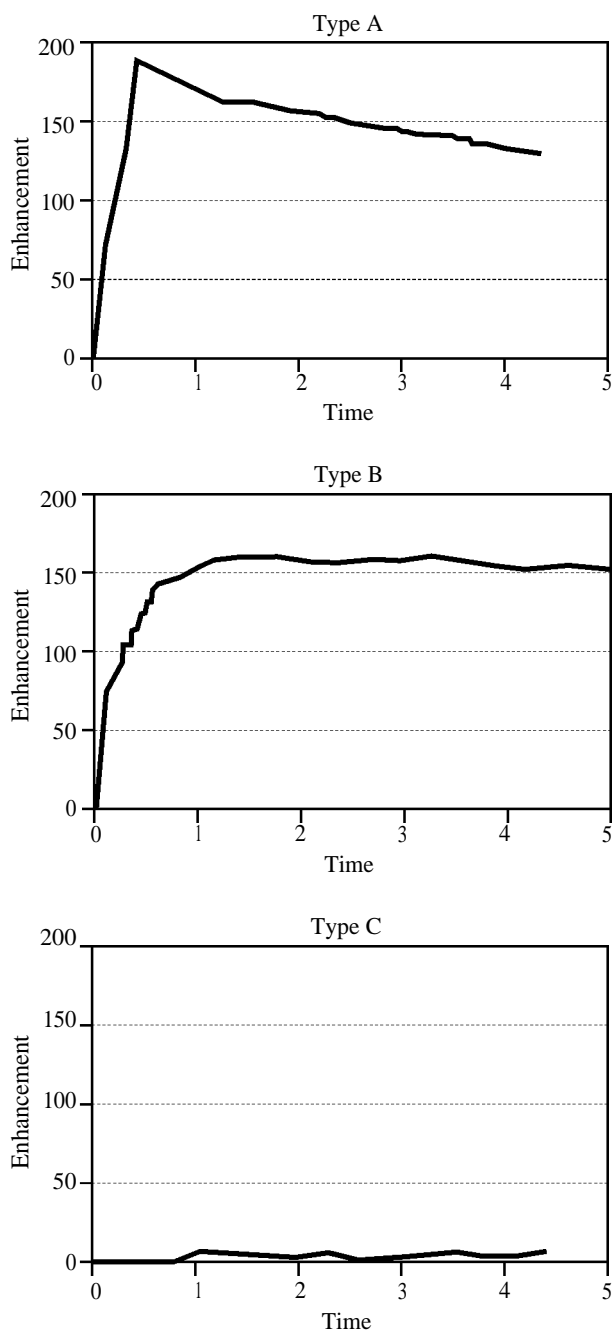


Fig. (1): Types of time-enhancement curve.

Results

In the present prospective study, we included 60 patients presented with pulmonary nodules (Table 1). The mean age of the included patients was 53.27±10.6 years, while the majority of patients were females (56.7%). Sixteen patients (26.7%) presented with metastatic breast cancer and twelve patients (20%) presented with metastatic cancer prostate.

Twelve patients (20%) presented with metastatic cancer pancreas and salivary gland, and eight patients (13.3%) presented with metastatic soft tissue and bony sarcomas of the extremities. Six patients (10%) have been diagnosed as primary lung cancer (4 cases) and lymphoma (2 cases). In six patients (10%), the histopathology examination, CT follow-up (doubling time) and associated imaging findings have confirmed that the nodules are benign, including granuloma (3 cases), hamartoma (2 cases) and rheumatoid nodules (1 case).

Regarding the anatomical site of the nodules, 28 patients (46.7%) had bilateral scattered pulmonary nodules. However, 12 patients (20%) had right upper lung lobe nodules and 6 patients (10%) had right lower lung lobe nodules. Moreover, 16 patients (23.4%) had left lung nodules. In terms of the multiplicity, 46.7% of the patients had multiple nodules Figs. (4,5) and 43.3% had single nodules. The size of the pulmonary nodules in this study was ranging from 1.5cm to 4cm.

The mean maximum net enhancement was 474 ± 94.4, and the slope of enhancement was 186.3 ± 13 (Table 2). The mean washout ratio was 5.45 ± 2.1%. The pattern of enhancement was homogenous in 50% of cases, heterogeneous in 40%, marginal in 6.7%, and non-enhanced in 3.3% of cases. Regarding the diffusion weighted MRI, the mean ADC value was 1.2±0.34 X 10⁻³ mm²/sec.

There were statistically significant differences between malignant and benign cases in terms of the maximum net enhancement (*p*=0.003) and ADC values (*p*<0.001) (Table 3). Malignant cases had significantly higher maximum net enhancement, washout ratio, and lower ADC values. There was no statistically significant differences between malignant and benign cases in terms of type of enhancement (*p*<0.42).

The maximum enhancement curve was a significant discriminator (Table 4), which yielded a sensitivity of 92.6% and specificity of 96% at a cut-off value of ≥375 Fig. (2). In contrary, the ADC value had poor diagnostic accuracy in differentiating between malignant and benign cases.

Table (1): Shows the baseline demographic characteristics of the included patients.

Variables	Patients (N=30)	
	No.	%
<i>Age in years:</i>	53.27± 10.6	
Mean ± SD	52 (42-62)	
Median (IQR)		
<i>Age group:</i>		
40-50	24	40
>50-60	18	30
>60-70	18	30
<i>Gender:</i>		
Male	26	43.3
Female	34	56.7
<i>Presentation:</i>		
Dyspnea, hemoptysis	6	10.0
Metastatic breast cancer	16	26.7
Metastatic cancer prostate	12	20.0
Metastatic cancer tail of pancreases	6	10.0
Metastatic salivary	6	10.0
Sarcoma of left arm	4	6.7
Sarcoma of left thigh	4	6.7
Unknown origin	6	10.0
<i>Serum creatinine (mg/dL):</i>		
Mean ± SD	0.863±0.21	
Median (IQR)	0.8 (0.7-1)	
<i>Serum urea (mg/dL):</i>		
Mean ± SD	20.97±6.88	
Median (IQR)	20 (16-22)	
<i>Plain X-ray findings:</i>		
Bilateral scattered nodules	28	46.7
Normal	16	26.7
Suspected	10	16.7
Unilateral nodule	6	10.0
<i>Number of nodules:</i>		
Multiple	28	46.7
Single	26	43.3
Two	6	10.0
<i>Site of nodules:</i>		
Bilateral	28	46.7
Left lower lung lobe	4	6.7
Left middle lung lobe	6	10.0
Left upper lung lobe	4	6.7
Right lower lung lobe	6	10.0
Right upper lung lobe	12	20.0

Table (2): MRI findings of the included patients.

Variables	Patients (N=30)	
	No.	%
<i>Max. net enhancement:</i>		
Mean ± SD	474±94.417	
Median (IQR)	450 (400-550)	
<i>Slope of enhancement:</i>		
Mean ± SD	186.3± 138	
Median (IQR)	100 (100-300)	
<i>Washout ratio:</i>		
Mean ± SD	5.45±2.17	
Median (IQR)	6 (0-12)	
<i>Enhancement curve HU:</i>		
Mean ± SD	62± 11.7	
Median (IQR)	60 (36-92)	
<i>Type of curve:</i>		
A	48	(80%)
B	8	(13.3%)
C	4	(6.7%)
<i>ADC value X 10⁻³ mm²/sec:</i>		
Mean ± SD	1.2±0.34	
Median (IQR)	1.2 (0.76-2)	
<i>Type of enhancement:</i>		
Homogenous	30	50
Heterogeneous	24	40
Marginal	4	6.7
Non-enhanced or faint	2	3.3

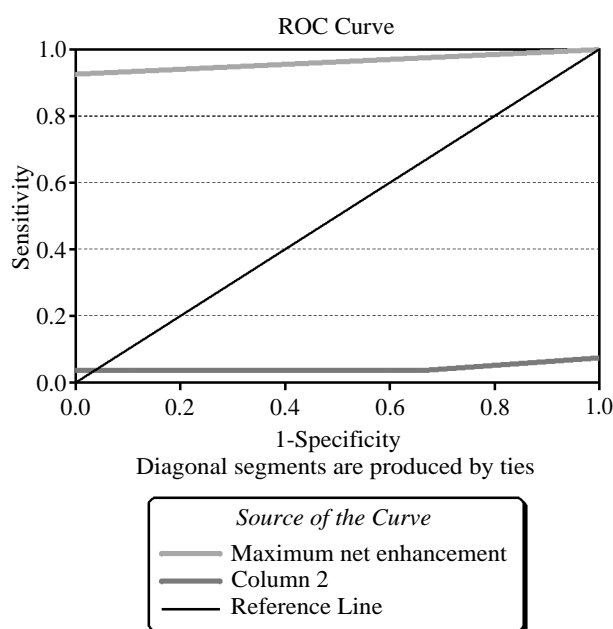


Fig. (2): The area under the curve and the diagnostic accuracy of ADC value and maximum enhancement curve in differentiating between malignant and benign cases.

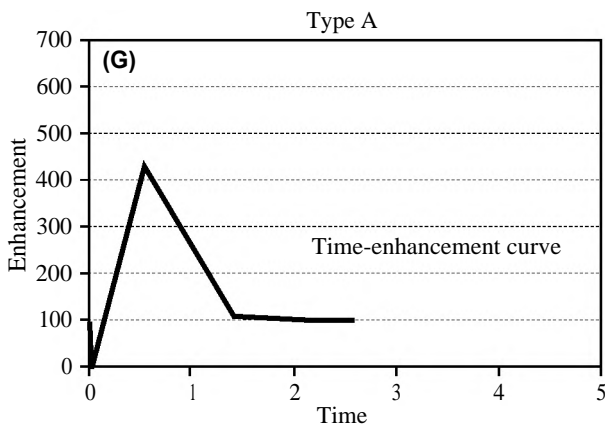
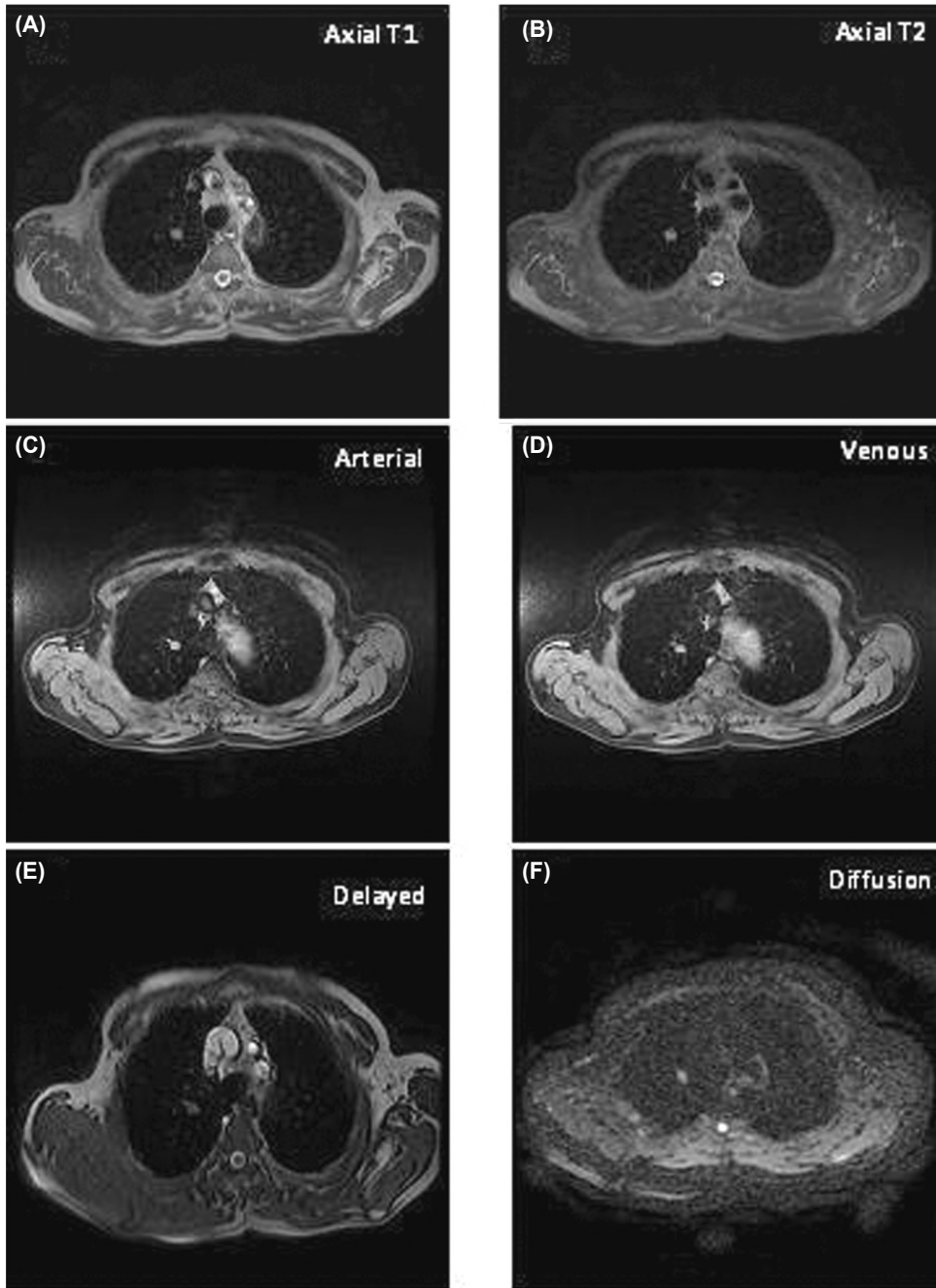


Fig. (3): A 70-year-old male and a known case of metastatic cancer prostate. His X-ray was unremarkable, and his MRI confirmed right upper lung lobe solitary pulmonary nodule with spiculated margin, which measured 1.5 X 1cm and displayed isointense signal intensity at T1WI (A) & T2WI (B) in addition to pretracheal LN measured 1 cm. After dynamic post contrast phases that lasts for 4 minutes, the nodule showed homogenous enhancement at arterial phase (C) and washout at delayed phases (D, E). The ADC value was $0.9 \times 10^{-3} \text{ mm}^2/\text{s}$ with restricted diffusion (F) (nodule is bright), and the time-enhancement curve was of type A (G).

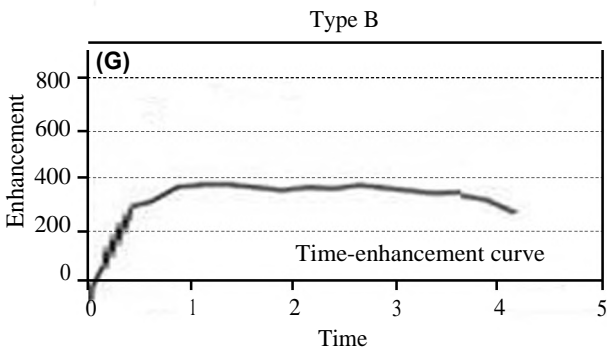
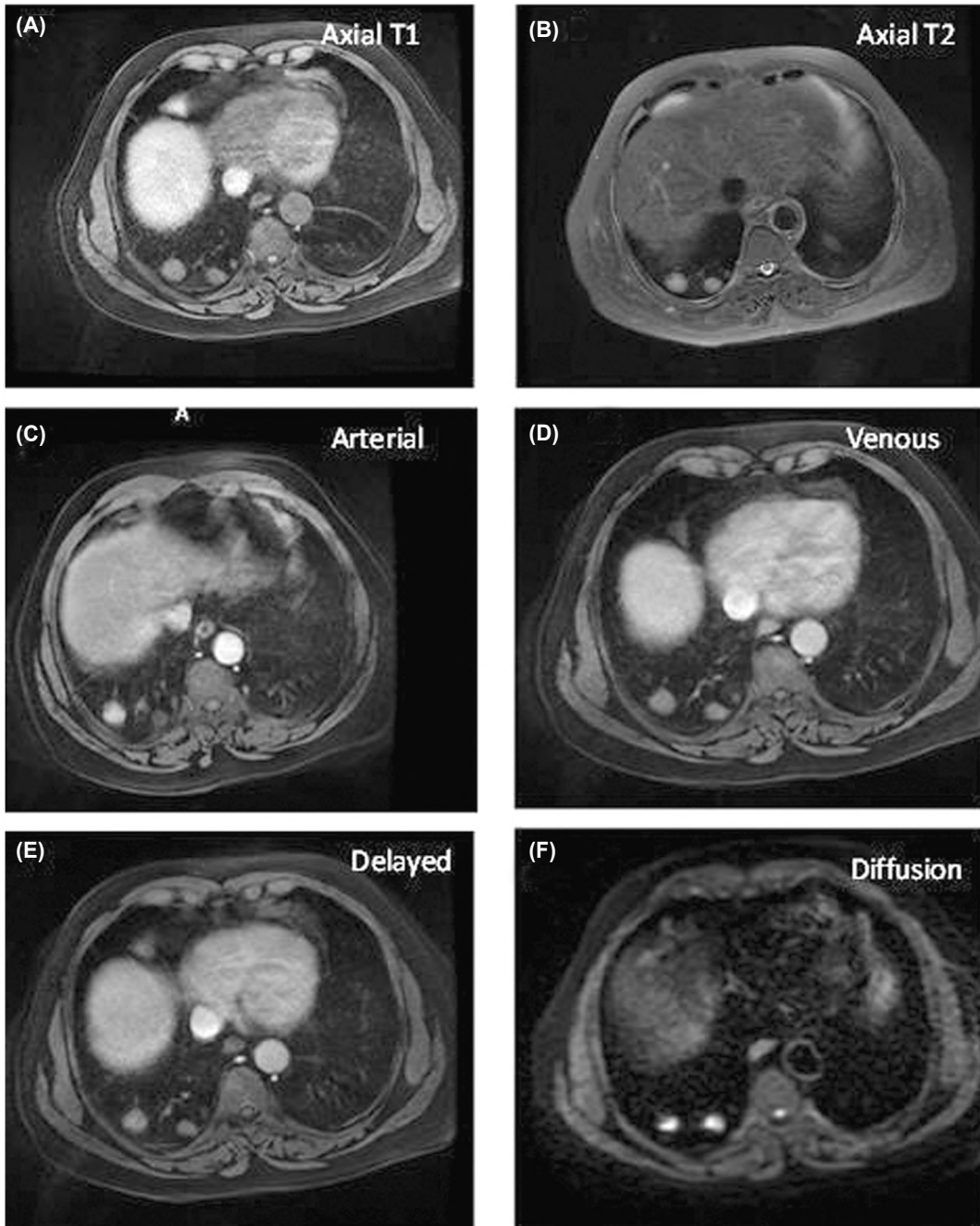


Fig. (4): A 62-year-old male and a known case of metastatic cancer prostate. His X-ray revealed suspected pulmonary nodules seen at the right lower lung zone. His MRI confirmed two pulmonary nodules at the right lower lung lobe with the largest one measured 2.2 X 1.8cm, and the other measured 1.5 X 1cm. The nodules displayed isointense signal at T1WI (A) & T2WI (B). After dynamic post contrast phases that lasts for 4 minutes, the nodules showed arterial enhancement (C) and washout at subsequent phases (D,E). The ADC value was $1.2 \times 10^{-3} \text{ mm}^2/\text{s}$ with restricted diffusion (F) (nodules are bright). The time-enhancement curve was of type B (G).

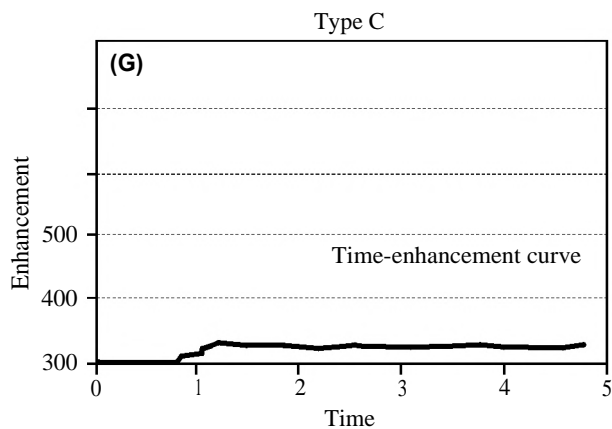
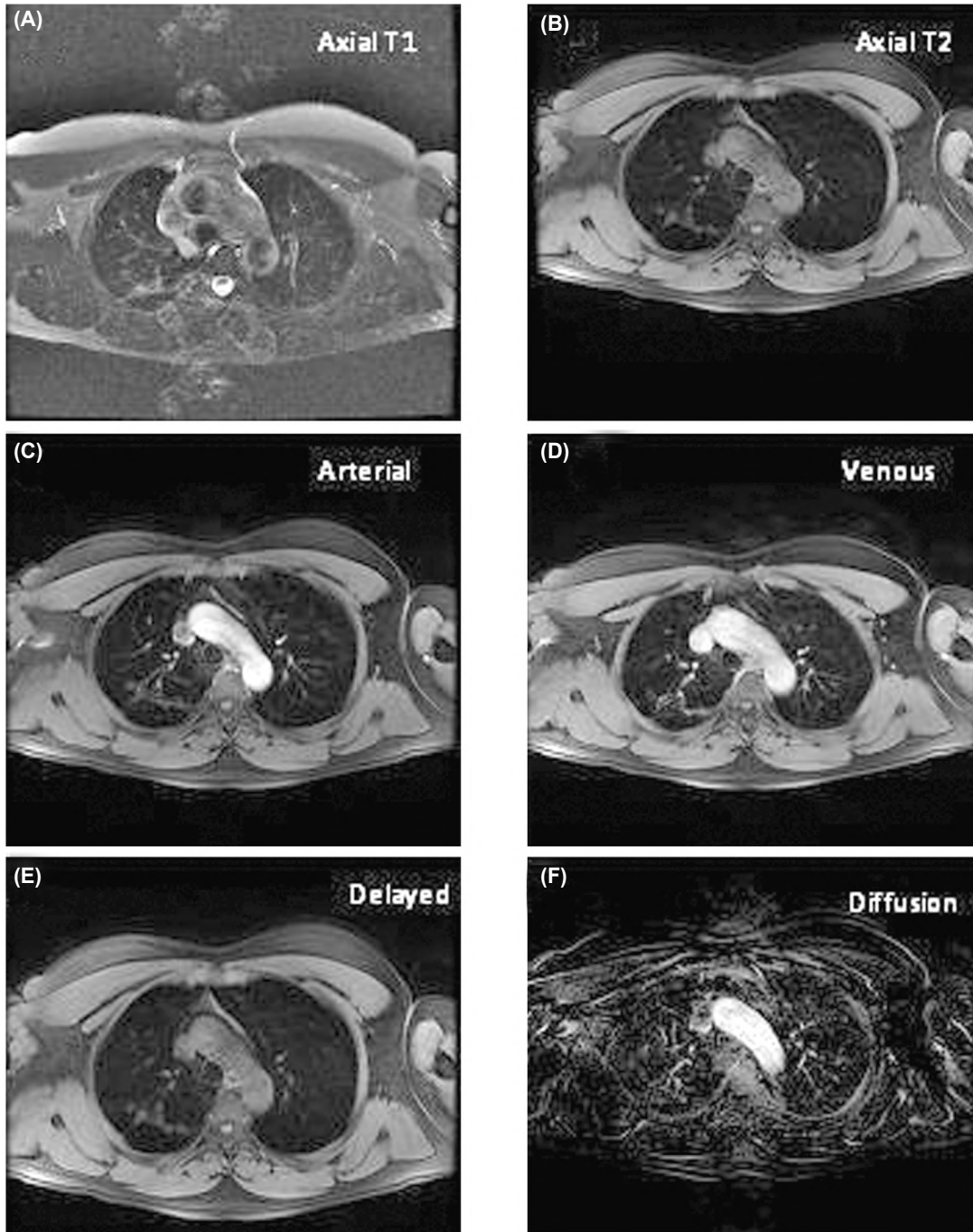


Fig. (5): A 41-year-old male with old TB infection complaining of dyspnea and hemoptysis. His X-ray revealed bilateral pulmonary nodules seen scattered on both lung fields. His MRI confirmed bilateral pulmonary nodules with the largest seen at the right upper lung lobe, which measured 1.8 X 1.6cm. The nodules showed isointense signal at T1WI (A) & T2WI (B). After dynamic post contrast phases that lasts for 4 minutes, the nodules showed faint arterial enhancement (C) with persistent enhancement at subsequent phases (no washout) (D,E). The ADC value was $2 \times 10^{-3} \text{ mm}^2/\text{s}$ with no evidence of restricted diffusion (F). The time-enhancement curve was of type C (G). CT examination revealed few bilateral calcified pulmonary nodules largest seen at right upper lung lobe representing old granulomatous infection.

Table (3): MRI findings according to pathology.

Variables	Malignant (N=54)	Benign (N=6)	p-value
<i>Max. net enhancement:</i>			
Mean ± SD	487.78±89	350±89	0.003
<i>Washout ratio:</i>			
Mean ± SD	5.82±1.28	4.01±2.39	0.04
Median (IQR)	6 (3-12)	4 (3-10)	
<i>ADC value X 10⁻³ mm²/sec:</i>			
Mean ± SD	1.14±0.47	1.9±0.1	<0.001
<i>Type of enhancement:</i>			
Homogenous	24 (44.4%)	6 (100%)	0.42
Heterogeneous	24 (44.4%)		
Marginal	4 (7.4%)		
Non-enhanced or faint	2 (3.7%)		

Table (4): Shows the area under the curve and the diagnostic accuracy of ADC value and maximum enhancement curve in differentiating between malignant and benign cases.

Variables	AUC, 95% CI	p-value	Cut-off points	Sensitivity	Specificity	PPV	NPV
ADC value	0.05 (0.01-0.11)	0.01	NA	NA	NA	NA	NA
Washout ratio	NA	NA	NA	NA	NA	NA	NA
<i>Max. net</i> enhancement	0.96 (0.89-0.99)	0.011	≥375	92.6%	96%	86.2%	81.5%

In terms of the outcomes of the present study, the dynamic contrast enhanced MRI showed that 90% of the pulmonary nodules were malignant. The histopathological examination confirmed that 90% of the lesions were malignant, and only 10% were benign. Consequently, the dynamic contrast enhanced MRI achieved a sensitivity of 93.1% and a specificity of 100% for the detection of the malignant pulmonary nodules.

Discussion

Accurate identification and characterization of the lung nodules is crucial for the early detection of lung cancer [8]. After detecting a lung nodule, the main goal for physicians is to identify that the nodule is suspicious enough to warrant further testing as early as possible and avoid unnecessary diagnostic or therapeutic procedures. Detection and follow-up using a Computed Tomography (CT) play an important role; however, there is a risk of false-positive results with CT, in addition to radiation exposure [9].

Over the past few decades, Magnetic Resonance Imaging (MRI) of pulmonary nodules has emerged as an alternative for CT [10]. Nevertheless, there is a scarcity in the published literature regarding the diagnostic utility of dynamic contrast enhanced MRI for detection of malignant pulmonary nodules. Therefore, we conducted the present cross sectional

study in order to evaluate the role of dynamic contrast enhanced MRI for the diagnosis of pulmonary nodules.

Regarding the age of the included patients, the mean age was 53.27±10.6 years. The majority of patients were females (56.7%). The female predominance in the present study can be attributed to a large number of patients with breast cancers [11].

In line with our findings, Yang and colleagues [12] retrospectively analyzed the clinical and imaging data of patients with pulmonary nodules who underwent CT guided needle biopsy from Jan. 2011 to March 2016. The mean age of the included patients was 55.41±11.94 years. Similarly, Shi and colleagues analyzed the role of the sizes of solitary pulmonary nodules in predicting their potential malignancies. The mean age of the included patients was 51.17±13.79 years, with a slight female predominance.

Regarding the nodule multiplicity, we found that 46.7% of the patients had multiple nodules and 43.3% had single nodules. The site of the nodules was bilateral in 46.7% of the cases. Likewise, Azhar and colleagues [13] performed a retrospective study to analyze the patient profile nodule characteristics of incidentally found pulmonary nodule.

The majority of patients had multiple bilateral nodules. Moreover, Caparica and colleagues [14] conducted a retrospective study from January 2011 to December 2013, and found that 51% of the patients had multiple nodules.

In this study, the dynamic contrast enhanced MRI achieved a sensitivity of 93.1% and a specificity of 100% for the detection of the malignant pulmonary nodules. This high diagnostic accuracy is related to the versatile parameters determined from signal intensity-time course curves. Malignant nodules showed stronger enhancement with a higher maximum peak, a faster slope and significant washout Fig. (3). Moreover, the paramagnetic contrast material effects in MRI depend on the interactions of the mobile water molecules in all tissue compartments, including the interstitium and cytoplasm, which give more details and information regarding the lesion characterization [15].

Our results have been in accordance with Alper and colleagues [16], who detected a stronger enhancement with higher median values of the early peak EP and maximum peak MP of the malignant than the benign lesions. There were significant differences between the benign and malignant lesions ($p < 0.001$). Sensitivity, specificity, positive predictive value and negative predictive value were 75, 93, 92 and 78% for EP and 93, 86, 88 and 93% for MP, respectively. Moreover, Schaefer and colleagues [17] had conducted a similar study on fifty eight patients, which revealed that the malignant nodules had a stronger enhancement with a higher maximum peak MP and a faster slope ($p < .001$).

All patients in our study had been undergoing routine follow-up CT scans in their original institutes to monitor the growth rate of the nodules and the Volume Doubling Time (VDT). The follow-up of the benign nodules showed stable size over time with long VDT, while the malignant fast growing lung nodules had shorter VDT < 232 days.

Despite that the comparison between the sensitivity and specificity of both CT and MRI has been beyond the scope of our study, the results of the histopathology examination have confirmed the VDT results. However, our dynamic MRI results proved to be more accurate and reliable, contrary to routine CT follow-up, which requires long time and repeated radiation exposure to differentiate the benign from the malignant nodules.

This has been in agreement with the prospective study of Kim and colleagues [18], who compared the diagnostic performances of MR imaging and CT. Eighty one patients with nodules (32 malignant,

49 benign) underwent dynamic MR imaging. The malignant nodules revealed significantly greater degrees of peak enhancement on dynamic MR imaging. In addition, Ohno and colleagues [19] prospectively compared the capabilities of CT and dynamic MRI, and their results have been in agreement with our study because they found significant differences in the maximum enhancement and slope of enhancement ratios between the malignant and benign nodules.

Nevertheless, other reports showed lower diagnostic performance of MRI than our study. Kono and colleagues [20] compared the dynamic contrast enhanced MRI of malignant and benign solitary pulmonary nodules. The characteristics of 202 solitary pulmonary nodules were reviewed retrospectively. With 110% or lower maximum enhancement ratio as a cut off value, the positive predictive value for malignancy was 92%, sensitivity 63% and specificity 74%. The exact causes of such heterogeneity are unclear; however, this difference can be attributed to different population's characteristics, or methodological differences [21].

Conclusion:

In conclusion, dynamic contrast enhanced MRI is valuable for diagnosis of pulmonary nodules and help in discrimination of benign from malignant ones. Moreover, dynamic MRI delineates significant kinetic and morphologic differences in vascularity and perfusion between malignant and benign solitary pulmonary nodules. The maximum net enhancement proved to be highly specific for malignancy.

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دور التباين الديناميكي المعزز للتصوير بالرنين المغناطيسي في تشخيص العقيدات الرئوية

المقدمة: أعتبر التمييز بين العقيدات الرئوية الحميدة والخبيثة تحدياً كبيراً لسنوات عديدة. على الرغم من حقيقة أن الخزعة والتقييم التسيجي أمران حاسمان للتشخيص النهائي، إلا أن طرق التصوير غير الجراحية الحديثة وأعادة في نتائجها.

الغرض من البحث: تهدف هذه الدراسة إلى تقييم دور التصوير بالرنين المغناطيسي المعزز بالتباين الديناميكي (DCE-MRI) في تشخيص العقيدات الرئوية.

المرضى وطرق البحث: هذه الدراسة عبارة عن دراسة مستعرضة أجريت على 60 مريضاً يعانون من عقيدات الرئة المحولة إلى قسم التشخيص والتصوير الراديوي من أقسام الصدر والأورام خلال الفترة من سبتمبر 2018 إلى سبتمبر 2019.

النتائج: كانت هناك فروق ذات دلالة إحصائية بين الحالات الخبيثة والحميدة من حيث الحد الأقصى الصافي للتحسين ($p=0.003$) وقيمة ($p < 0.001$). كان متوسط التحسين الصافي الأقصى 94.417 ± 474 ، وكان متوسط معدل الغسل 2.17 ± 5.45 ، وكان متوسط قيمة التحسين الأقصى $1.2 \pm 0.34 \times 10^{-3}$ م²/ثانية. كانت الحالات الخبيثة أعلى بكثير من التحسين الصافي، ونسبة الغسل، وإنخفاض قيم ADC. كان منحني التحسين الأقصى تميزاً كبيراً، والذي أنتج حساسية 92.6% وخصوصية 96% بقيمة قطع cut 375. على العكس من ذلك، كانت قيمة ADC دقة تشخيصية ضعيفة في التفريق بين الحالات الخبيثة والحميدة.

الملخص: يعد التصوير بالرنين المغناطيسي المعزز بالتباين الديناميكي ذو قيمة لتشخيص العقيدات الرئوية والتمييز الحميد من الخبيث.