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Role of Multi-Slice Computed Tomography Perfusion in Evaluation of the Pulmonary Nodules

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Abstract: The current study aim is the role of multi-slice CT perfusion in assessment of pulmonary nodules. Eighty patients with pulmonary nodules underwent non contrast CT scan of the chest and dynamic CT perfusion of the chest. Dynamic CT chest perfusion of 80 patients with pulmonary nodules revealed 24 patients had benign nodules of low biological activity, 16 patients had benign nodules of high biological activity and 40 patients had malignant nodules (16 of them had multiple nodules in both lung fields and clinical history of primary extra pulmonary malignancy, so diagnosed as metastatic nodules). Perfusion flow, extraction fraction and blood volume; these indexes showed significant differences between malignant nodules and benign nodules with low biologic activity (P>0.0001) In addition, these indexes showed a significant difference between benign nodules with high biologic activity and those with low biologic activity (P>0.0001) and the perfusion flow was of high benefit for nodules characterization than ejection fraction and blood volume by the higher significant values. CT perfusion compared the effect of therapy (chemotherapy and or radiotherapy) on metastatic pulmonary nodules before and after start of treatment by perfusion parameters (perfusion flow, extraction fraction and blood volume) & colour maps with the clinical data and follow up revealed that both results closely near and raise the efficacy of CT perfusion study in follow up and assessment of treatment response in metastatic pulmonary nodules. It can be concluded that CT perfusion is a feasible non-invasive diagnostic technique able to evaluate the nature of pulmonary nodules and treatment response in patients with metastatic pulmonary nodules.

Keywords: CT Perfusion, Perfusion Flow, Extraction Fraction

1. Introduction

Pulmonary nodules are defined by Fleischner Society on chest radiographs and CT scans as "rounded opacities, well or poorly defined, measuring up to 3 cm in diameter" & pulmonary nodules were classified into three main groups: malignant nodules, benign nodules with low biologic activity and benign nodules with high biologic activity [1, 2].

The role of diagnosis is to allow treatment strategies in all patients with treatable malignant nodules and to avoid unnecessary thoracotomy in those patients with benign lesions. So, it is essential that one be able to differentiate malignant from benign nodules in the least invasive manner and it is difficult to directly identify between malignancy and benignancy of peripheral pulmonary nodule by using morphology features because of changes in the blood vessel volume, perfusion and capillary permeability in new tumor vessels which may result in the changes of blood patterns [3, 4].

It has been hypothesized that malignant and benign pulmonary nodules have distinctly different physiologic, metabolic, and pharmacokinetic characteristics. Attempts have been made to differentiate these two nodule types with dynamic single-detector helical and multi-detector computed

tomography (CT), dynamic magnetic resonance (MR) imaging, and positron emission tomography (PET) or combined PET/CT with use of fluorine 18 fluorodeoxyglucose (FDG) [3, 5].

Multi-detector CT assessment of the regional CT perfusion parameters of lung cancer and/or lung parenchyma have been proposed & Dynamic first-pass area-detector perfusion CT is more specific and accurate than PET/CT for differentiating malignant from benign pulmonary nodules, by Utilizing the 320-row system, the recent dynamic volume CT mode makes it possible to include the pulmonary artery, the aorta, and the tumour studied in one gantry rotation without table movement. Then contrast-enhanced dynamic volume acquisitions will simultaneously capture the pulmonary and systemic circulation input functions as well as the tumour's first-pass response function [2, 6, 7].

Perfusion imaging can detect the differentiation of blood supply between benign and malignant pulmonary nodules in quantity and quality, Due to tumor angiogenesis, malignant pulmonary lesions has high regional blood flow, blood volume and consecutively contrast-enhancement. Perfusion and vascular permeability Changes can be assessed by dynamic contrast-enhanced CT, which is based on the analysis of time-density curves acquired with consecutive scans after injection of a bolus of iodinated contrast material, So accurate characterization of pulmonary nodules can be obtained by the use of Dynamic first-pass area-detector perfusion CT parameters like perfusion flow (PF), Extraction fraction (EF) and blood volume. [2, 7, 8].

2. Patients and Methods

2.1. Patients

Eighty patients presented with pulmonary nodule either associated by primary tumor in other site in the body and the pulmonary nodule is suspected to be metastatic, vague clinical data confusing infection and neoplastic nodule or difficult accessible pulmonary nodule with biopsy. during the period between May 2016 to Feb. 2018.

Patients were excluded from the study if they have known hypersensitivity to contrast media, patients with creatinine level more than 2 mg/dl or pregnant women. Approval of research ethics committee (REC) and informed written consent were obtained from all participants in the study after full explanation of the benefits and risks of the procedure. Privacy &confidentiality of all patient data were guaranteed. All data provision were monitored and used for scientific purpose only.

2.2. Method

All Patients were Subjected to the Following.

2.2.1. Full History Taking and Clinical Examination

Onset, course and duration of the present illness, History of other systemic diseases, general and local examination.

2.2.2. Laboratory Investigation

Serum creatinine level was estimated in all patients to assess the renal function before the usage of contrast media.

2.2.3. Patient Preparation

Patient is receiving IV contrast, they should not eat or drink 4 hours prior to exam. Patients were asked to remove jewelry and other metallic objects that might interfere with the scan. Prior to the administration of iodinated contrast, patients are screened for previous reactions to iodinated contrast media, history of diabetes, kidney disease, pheochromocytoma, solitary kidney or myeloma.

2.2.4. Image Acquisition and Processing

CT perfusion study was performed with 320- detector row CT (Aquilion ONE; Toshiba medical systems, Ohtawara, Japan) Conventional low radiation-dose CT images of the entire lung were obtained from the lung apex to the diaphragm during suspended respiration at the end of inhalation. All conventional CT examinations were performed with volumetric scanning by using the step-and-shoot technique (i.e., wide volume scanning) with the following parameters: (256–320) 3 0.5-mm collimation, 120kVp, 160 mA, a 0.5-second gantry rotation time, a 512 3 512 matrix, and a 300–350-mm field of view with three to four time scans.

i. Contrast Material

A dual-head power injector was used for the bolus administration of 20–40mL (0.2mL per kilogram of body weight) of iodinated contrast material (iopamidol, Iopamiron 300; Bayer Healthcare) via a cubital vein at a rate of 5 mL/sec, which was followed by the administration of 20mL of saline solution at the same rate.

ii. Dynamic CT Acquisition

Dynamic first-pass area-detector CT performed through the nodule within a 16-cm area by using the following parameters: 320 3 0.5-mm collimation, 80kVp, 120 mA, a 0.5-second gantry rotation time, a 512 3 512 matrix, and a 300–350-mm field of view. All dynamic area-detector CT images were reconstructed with a filtered back-projection type cone beam reconstruction algorithm (ConeXact; Toshiba Medical Systems) for 2-mm section thickness reconstruction.

All dynamic area-detector CT data were first acquired every 2 seconds, for 28 seconds, during breath holding at the end of inhalation; then, an additional five series of data were obtained with breath holding at the end of inhalation-at 40, 50, 60, 90, and 120 seconds. Thus, a total of 19 image series were obtained (at 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28, 40, 50, 60, 90, and 120 seconds).

To accurately obtain time density curves of tissue from the first pass of contrast agent, CT scans are acquired at high temporal resolution (e.g., one image per second).

iii. Image Processing

The CT images were analyzed using software (Body perfusion; Toshiba Medical Systems) with generation of color functional maps and calculation of functional parameters. Respiratory mis registrations were compensated automatically using software (Body registration; Toshiba

Medical Systems).

Dual input CT perfusion: Region of interest (ROIs) were placed on the aorta for measuring the arterial input function, on the pulmonary artery, left atrium & on lung tissue with evaluation of the following perfusion parameters:

1. Time density curve (TDc).
2. Perfusion flow (PF).
3. Extraction fraction (EF).
4. Blood volume (PV).

The perfusion parameters will be calculated in the area of pulmonary nodule and in the surrounding lung parenchyma.

Single input CT perfusion: Region of interest (ROIs) were placed on the aorta & on the lung tissue. Next Equivalent blood volume & Flow extraction product maps display overlaid on CT images.

iv: Image Analysis (interpretation)

Depending on perfusion parameters (perfusion flow, extraction fraction and blood volume) and color maps, the three categories of pulmonary nodules determined according to the following:

1. High perfusion flow, extraction fraction and blood volume with mainly red colours in colour scale denoting malignant nodule.
2. Intermediate perfusion flow, extraction fraction and blood volume with mixed green yellow colors in color scale denoting high biologically active nodule.
3. Low perfusion flow, extraction fraction and blood volume with mainly blue colours in colour scale denoting low biologically active nodule.

V: Statistical Methods

The collected data were organized, tabulated and statistically analyzed using SPSS software (Statistical Package for the Social Sciences, version 19, SPSS Inc. Chicago, IL, USA). For quantitative data, the range, mean, standard deviation and median were calculated. For qualitative data, which describe a categorical set of data by frequency, percentage or proportion of each category, comparison between two groups and more was done using Chi-square test (χ^2 test). For comparison between more than two means of parametric data, F value of ANOVA test was calculat.

3. Results

This study included eighty patients (60 males and 20 females) with age range (45-60 years) with mean (51.4 ± 4.53). All of them had pulmonary nodules.

Table 1. *The morphology of pulmonary nodules in the studied patients (n= 80 patients).*

The shape of the lesion	No of patients	%
Speculated	8	10
Lobulated	52	65
Circumscribed rounded	20	25

As regard the shape of the pulmonary nodules lobulated appearance the most frequent shape.

Table 2. *Nature of pulmonary nodules by CT perfusion technique among the studied patients.*

Nature of lung nodule	No. of patients	%
-Benign nodules with low biological activity	16	20
-Benign nodules with high biological activity	24	30
-Malignant nodules	40	50
*Primary malignant	8	10
*Secondary malignant	32	40

Depending on the combination of colour maps obtained by CT perfusion technique, radiological configuration (shape and border of the pulmonary nodules) and clinical data & follow up of these patients, classification of the eighty patients into three groups was done, 24 patients were diagnosed as being benign nodules with low biological activity, 16 patients were diagnosed as being benign nodules with high biological activity and 40 patients were diagnosed as being malignant nodules (32 patients of them had multiple nodules in both lung fields and clinical history of primary extra pulmonary malignancy, so diagnosed as metastatic nodules).

Table 3. *Perfusion flow values (ml/min/100ml) in the pulmonary nodules and the surrounding normal lung parenchyma.*

Perfusion flow	Pulmonary nodule	Normal lung parenchyma
Range	5.5 – 97.6	4.2 – 10.5
Mean ± SD	67.42 ± 35.74	7.13 ± 3.41
T. test	10.652	
P. value	0.001*	

It was found that the value of perfusion flow in the differentiation between the pulmonary nodules & the surrounding lung parenchyma is statistically significant (P<0.001) as it was significant higher in pulmonary nodules (mean value 67.42 ± 35.74 ml/min/100ml) if compared to surrounding lung parenchyma. (7.13 ± 3.41 ml/min/100ml).

Table 4. *Extraction fraction values (ml/min/100ml) in the pulmonary nodules and the surrounding normal lung parenchyma.*

Extraction fraction	Pulmonary nodule	Normal lung parenchyma
Range	0.8 – 18.4	0.5 – 0.8
Mean ± SD	9.74 ± 4.37	0.71 ± 0.13
T. test	13.054	
P. value	0.001*	

It was found that the value of extraction fraction in the differentiation between the pulmonary nodules & the surrounding lung parenchyma is statistically significant (P<0.001) as it was significant higher in pulmonary nodules (mean value 9.74 ± 4.37 ml/min/100ml) if compared to surrounding lung parenchyma (mean value 0.71 ± 0.13 ml/min/100ml).

Table 5. *Blood volume values (ml/100ml) in the pulmonary nodule and the surrounding normal lung parenchyma.*

Blood volume	Pulmonary nodule	Normal lung parenchyma
Range	0.9 – 7.24	0.4 – 0.9
Mean ± SD	4.13 ± 2.64	0.67 ± 0.24
T. test	8.234	
P. value	0.001*	

It was found that the values of blood volume in the differentiation between the pulmonary nodules & the surrounding lung parenchyma is statistically significant (P<0.0001) as it was significant higher in pulmonary nodules (mean value 4.13 ± 2.64 ml/100ml) if compared to the surrounding lung parenchyma (mean value 0.67 ± 0.24ml/100ml).

Table 6. *Ranges and Mean values of Perfusion flow, extraction fraction & Blood volume in low biologically active benign nodules, high biologically active benign nodules and malignant nodules.*

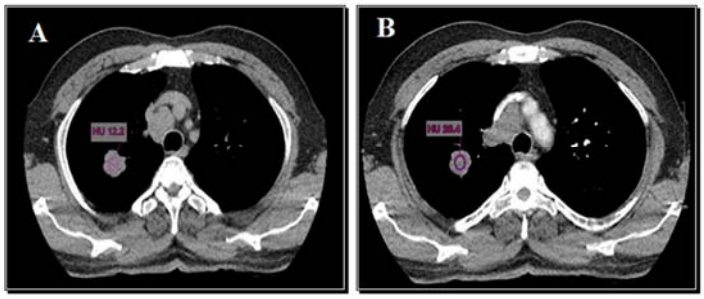
Measurement values	The studied patients with pulmonary nodules (n=40)			F-test	P
	Malignant nodules	Low biologically active benign nodules	High biologically active benign nodules		
	Range Mean	Range Mean	Range Mean		
Perfusion flow (ml/min/100ml)	67 – 97.5 81.5 ± 21.6	5.5 – 16.4 9.3 ± 4.2	35.5 – 61.8 44.4 ± 13.63	8.452	0.001*
Extraction Fraction (ml/min/100ml)	5.6 – 18.4 11.0 ± 7.6	0.8 – 1.8 1.2 ± 0.4	1.1 – 4.3 2.1 ± 0.95	7.325	0.001*
Blood volume (ml /100ml)	3.54 – 7.24 6.2 ± 2.4	0.9 – 2.5 1.1 ± 0.5	1.9 – 6.3 4.1 ± 1.9	6.987	0.001*

It was found that perfusion parameters calculated were significantly different between malignant nodules, high biologically active nodules and low biologically active nodules (P<0.0001) as there were significant increase in perfusion flow, ejection fraction and blood volume in malignant nodules rather than high biologically active nodules and low biologically active nodules.

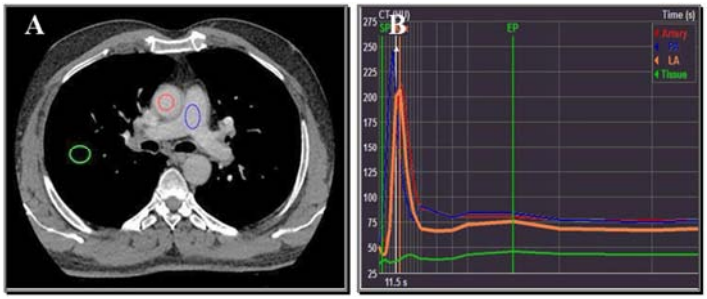
Table 7. *Treatment response assessed by computed tomographic perfusion imaging (CT) and clinical data among the studied metastatic nodules (n=32).*

Treatment response	The studied patients with metastatic nodules (n=16)				χ^2	P
	CT perfusion results		Clinical data results			
	N	%	N	%		
Complete response	8	50	7	43.75		
Partial response	4	25	3	18.75	0.613	0.737
Poor response	4	25	6	37.5		

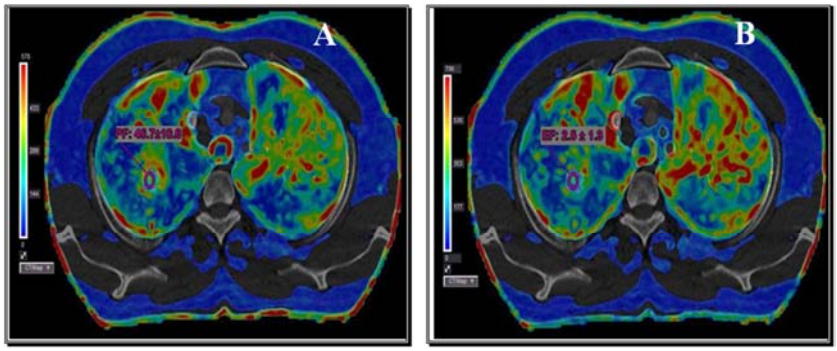
It was found that effective treatment according to the previously mentioned perfusion parameters (perfusion flow, extraction fraction and blood volume) and colour maps was reported in 8 patients with metastatic nodules, residual malignant activity was reported in 4 patients and poor response was reported in also 4 patients & the clinical data reported by the follow up of these patients after the start of treatment regimen by the clinician confirm these results and these results raise the efficacy of CT perfusion study in the follow up and assessment of treatment response in metastatic pulmonary nodules.



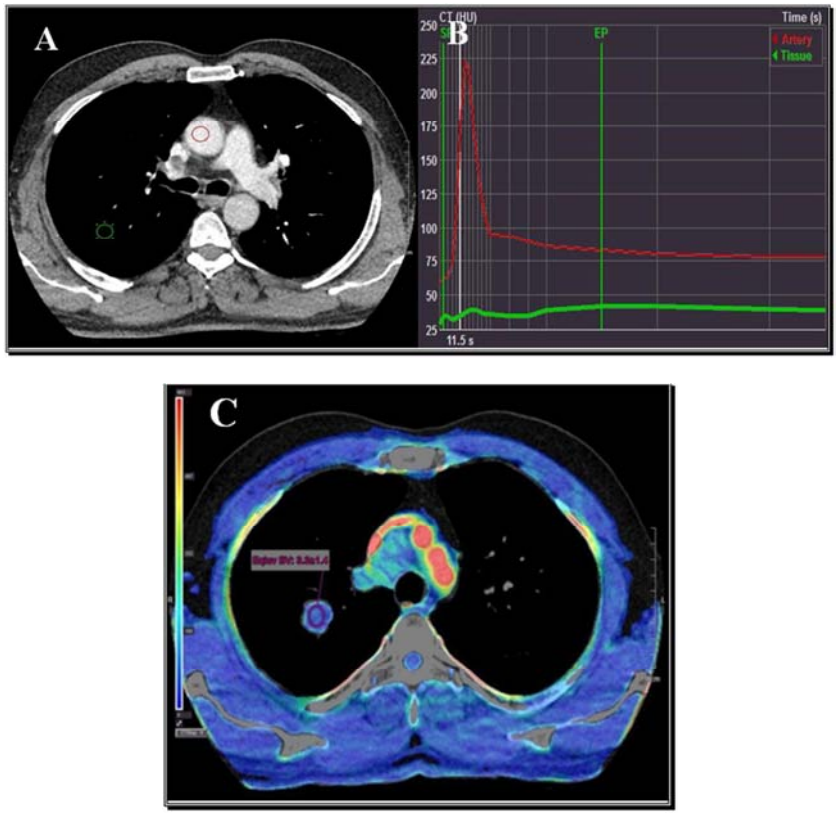
A&B Axial CT study of the chest (before and after contrast respectively) revealed a single pulmonary nodule at the posterior segment of right upper lung lobe with increased hounsenfield unit less than 20 units (from 12.2 to 26.4 HU)



Dual input CT perfusion of the lung: A- Axial CT image shows selection of ROI on aorta, pulmonary artery and lung tissue B- Time density curve.

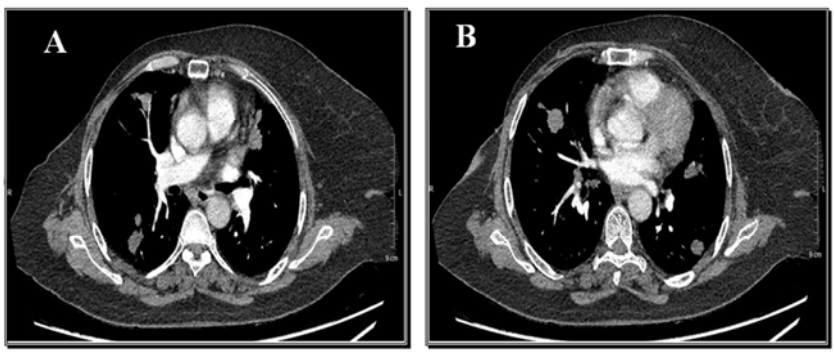


Dual input CT perfusion of the lung: A-Perfusion flow= 45.7±10.6 ml/min/100ml &B- Extraction fraction= 2.5±1.3ml/ min/ 100ml…. Means moderately high perfusion flow and fraction.

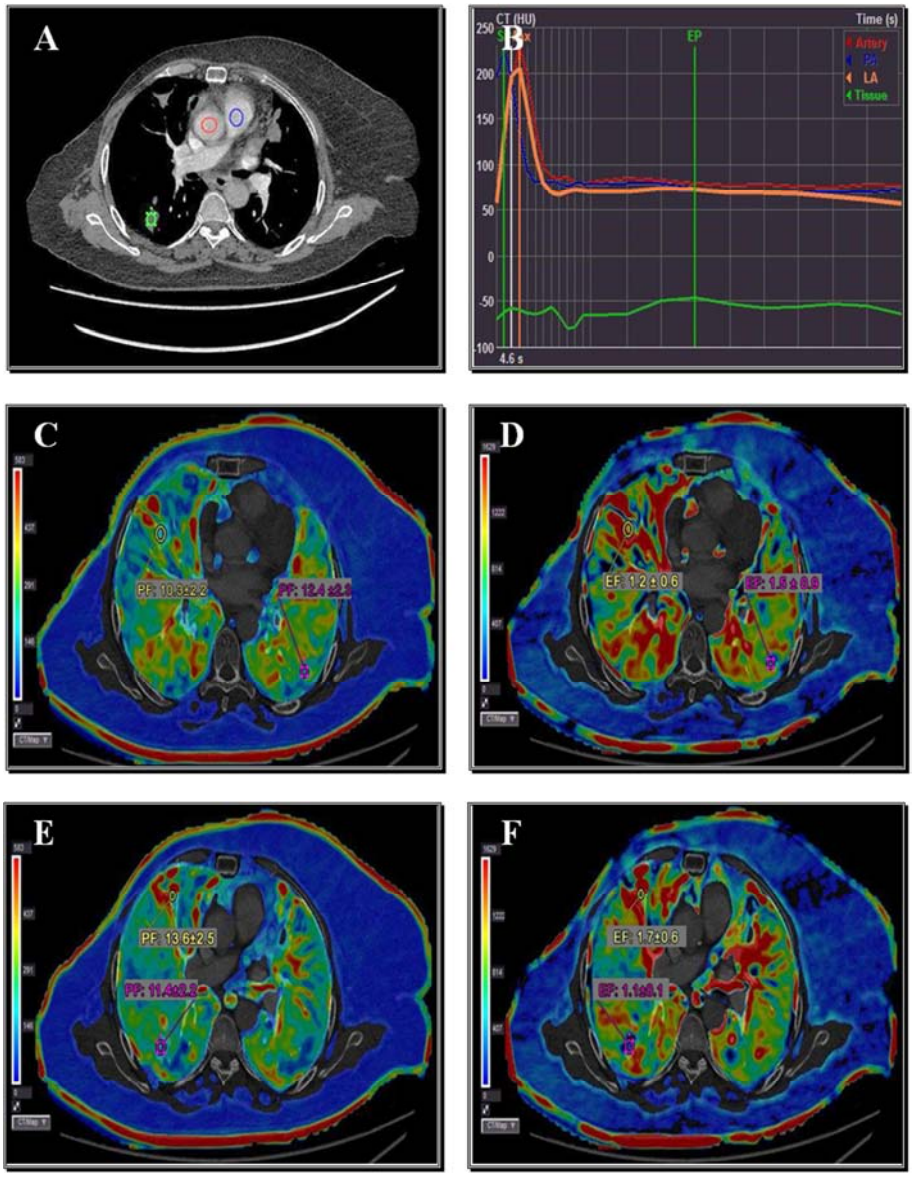


Single input CT perfusion of the lung: A- Axial CT image showed selection of ROI on aorta and lung tissue B- Time density curve &C- Axial functional equivalent blood volume perfusion colored map showed Equiv BV: 3.3±1.4 ml/100ml, Consistent with moderately increased in blood volume, according to color scale, the nodule show mixed green yellow colors. Means high biologically active nodule.

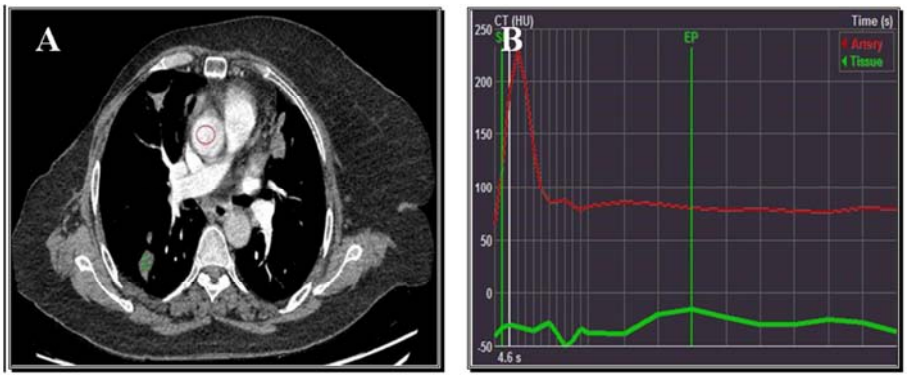
Figure 1. *Male patient aged 49 years complaining of dyspnea and cough for 2 months with Benign nodule of high biological activity.*

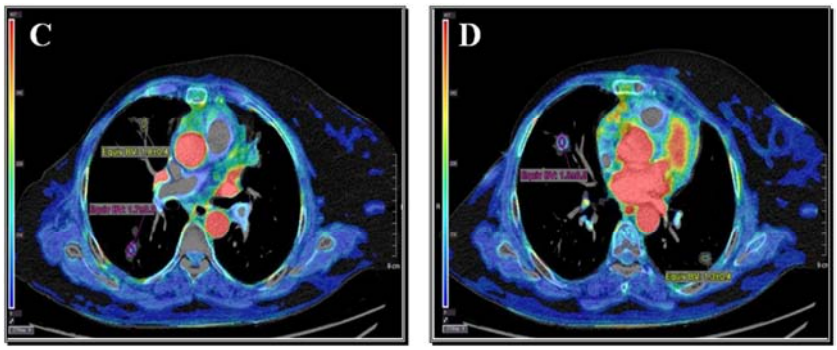


A&B-Axial CT study of the chest with contrast respectively revealed two pulmonary nodules at the anterior segment of right upper lung lobe, apical segment of right lower lung lobe and two nodules at the lateral segment of middle lobe and posterior segment of the left lower lung lobe.



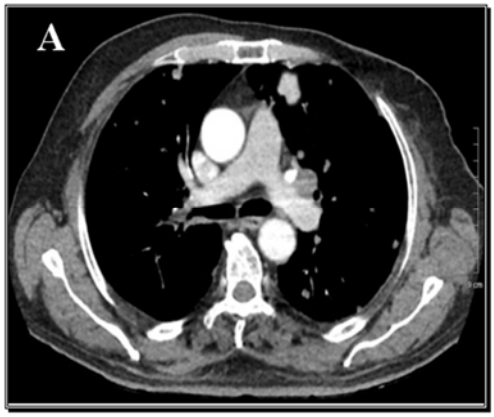
Dual input CT perfusion of the lung:- A-Axial CT image showed selection of ROI on aorta, pulmonary artery and lung tissue B-Time density curve, C&D-Perfusion parameters of the two pulmonary nodules at the right upper and middle lung lobe respectively (Perfusion flow 10.3±2.2 & 12.4 ±2.3 ml/min/100ml & Extraction fraction 1.2± 0.6 & 1.5± 0.9 ml/ min/ 100ml)E&F-Perfusion parameters of the other two pulmonary nodules at the right & left lower lung lobe respectively (Perfusion flow 13.6±2.5 & 11.4 ±2.2 ml/min/100ml & Extraction fraction 1.7± 0.6 & 1.1± 1.1 ml/ min/ 100ml)Means low perfusion flow and extraction fraction.



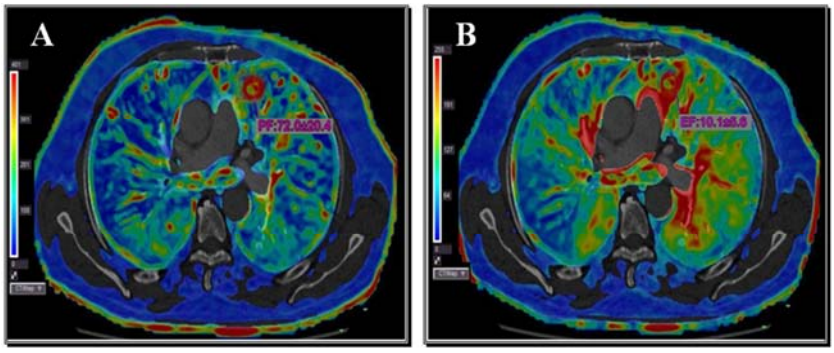


Single input CT perfusion of the lung:A - Axial CT image showed selection of ROI on aorta and lung tissue, B- Time density curve, C- Axial functional equivalent blood volume perfusion colored map of the right upper and middle lobes pulmonary nodules Equiv BV: 1.3±0.4 ml/100ml & 1.3±0.5 ml/100ml and D- axial functional equivalent blood volume perfusion colored map of the other two right and left lower pulmonary nodules Equiv BV: 1.8±0.4 ml/100ml & 1.7±0.3 ml/100ml.. Consistent with decreased blood volume & according to color scale the nodules show blue color means low grade biologically active nodules.

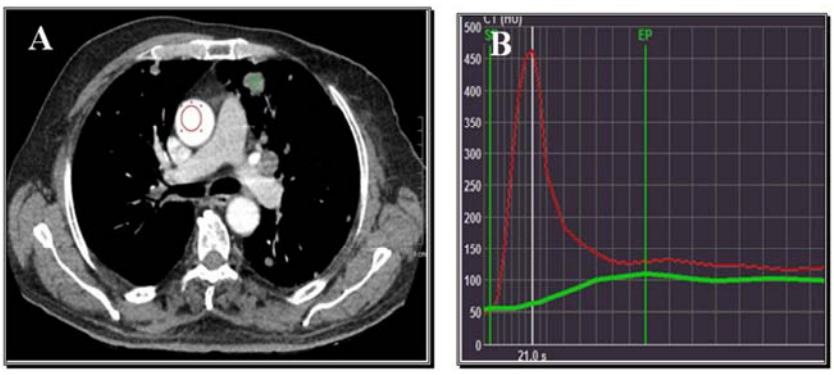
Figure 2. *A case of cancer breast underwent right mastectomy with Multiple low biologically active pulmonary nodules.*

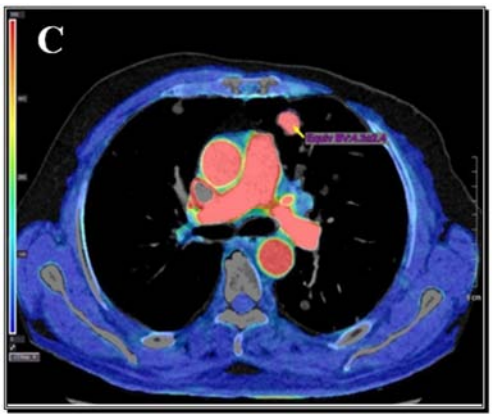


A-Axial CT study of the chest with contrast revealed a single pulmonary nodule at the anterior segment of left upper lung lobe.



Dual input CT perfusion of the lung:- A-Perfusion flow of the nodule = 72.0±20.4 ml/min/100ml & B-Extraction fraction 10.1± 5.6 ml/ min/ 100ml, Means increased perfusion flow and Extraction fraction.





Single input CT perfusion of the lung: A-Axial CT image showed selection of ROI on aorta and lung tissue B-Time density curve, C-axial functional equivalent blood volume perfusion colored map showed Equiv BV: 4.3±2.4 ml/100ml, Consistent with increased blood volume, on colour scale; the nodule has mainly red colour means malignant nature of the nodule.

Figure 3. *Male patient aged 60 years complaining of hemoptysis with Malignant pulmonary nodule.*

4. Discussion

The differentiation of pulmonary nodules as benign or malignant remains a diagnostic challenge for thoracic radiology. During the past decade, promising results for more specific differentiation of malignant and benign nodules using dynamic contrast material-enhanced CT have been reported [9].

Nevertheless, current technological advances in multi-detector row CT (MDCT), specifically sequential volume acquisition and data processing, allow for more accurate evaluation of tissue hemodynamics than that attainable with previous CT techniques [10].

Techniques in these studies rely on single-level acquisition with long time intervals, which were considered to be problematic for quantitative assessment of whole tumor perfusion because the blood flow within tumours is spatially and temporally heterogeneous [11].

In our study, we have evaluated the diagnostic qualitative and quantitative role of the multi-detector computed tomographic perfusion imaging in assessment of different types of pulmonary nodules and evaluation of therapeutic response of the metastatic nodules.

In the current study we examined 80 patients with pulmonary nodules. All these patients were Firstly underwent conventional CT scan to find the tumor and determine the section of perfusion scan. Then dynamic contrast enhanced perfusion imaging was done and by using the perfusion parameters (perfusion flow, ejection fraction and blood volume), colour maps and time density curves, different types of pulmonary nodules are evaluated.

In our study the most frequent shape of pulmonary nodules among the studied patients was the lobulated pattern (52 patients) constitutes 65% of all patients but not all the lobulated pulmonary nodules in our study were benign.

This result was in agreement with Swensen et al., (2000) [12] who reported that Using standard contrast-enhanced CT, the characterization of pulmonary nodules is based on simple morphological criteria e.g., irregular or spiculated margins as a sign for malignancy or calcifications as a sign of benignity. However, in a clinical context these simple morphologic criteria are unreliable for an accurate differentiation between benign and malignant lung nodules.

Also Erasmus et al., (2000) [13] says that, there is overlap between benign and malignant nodules in terms of morphology in many cases. 25-39% of malignant nodules are inaccurately classified as benign after radiologic assessment of size, margins and internal characteristics.

In our study by the combination of colour maps obtained by CT perfusion technique, radiological configuration (shape and border of the pulmonary nodules) and clinical data & follow up of these patients, classification of the forty patients into three groups was done, 24 patients were diagnosed as being benign nodules with low biological activity, 16 patients were diagnosed as being benign nodules with high biological activity and 40 patients were diagnosed as being malignant nodules (32 patients of them had multiple nodules in both lung fields and clinical history of primary extra pulmonary malignancy, so diagnosed as metastatic nodules).

This was in agreement with Callister et al., (2015) [14] who reported that, when interpreting DCE-CT it is essential that the mean nodule enhancement is interpreted in the context of the clinical history and the morphological appearances of the nodule. The clinical history should provide information about the pre-test probability for malignancy.

In our study we found the total perfusion flow, extraction fraction and blood volume; these indexes showed significant differences between malignant nodules and benign nodules with low biologic activity ($P<0.0001$) In addition, these indexes showed a significant difference between benign nodules with high biologic activity and those with low biologic activity ($P<0.0001$) and the perfusion flow was of high benefit for nodules characterization than ejection fraction and blood volume by the higher significant values.

These results was in line with Sitartchouk et al., (2009) [15] who reported that, the better PF MS (perfusion flow by maximal slope method) results compared with the EF PP

(extraction fraction by patlak plot method) and/or BV PP results (blood volume by patlak plot method) because the mathematical algorithm of the maximum slope model is simpler than that of the patlak plot model and is considered to be more tolerant of errors derived from image noise, contrast material administration, body weight, cardiac output, and/or the data acquisition temporal resolution. Therefore, the more accurate positive and negative predictive values of PF MS at dynamic area-detector CT, as compared with those of the EF PP and BV PP calculated from dynamic area-detector CT data, could help physicians provide immediate treatment for patients with malignant nodules and help avoid surgery or further intervention for patients without malignant nodules.

In the current dynamic CT perfusion study we compared the effect of therapy (chemotherapy and or radiotherapy) on metastatic pulmonary nodules before and after start of treatment by perfusion parameters (perfusion flow, extraction fraction and blood volume) & colour maps with the clinical data and follow up of these patients and we found that both results were closely near to each other and these results raise the efficacy of CT perfusion study in the follow up and assessment of treatment response in metastatic pulmonary nodules.

The findings in this work are also consistent with Garcia-Barros et al., (2003) [16] who reported that, besides the differentiation of benign and malignant nodules, dynamic contrast-enhanced CT may be used for the assessment of tumor response to targeted therapy or radiotherapy. It has been reported that microvascular damage is a key mechanism in tumor response to radiation. Therefore, reduced volume of the vascular bed following radiation therapy would be reflected by reduced blood flow, blood volume.

5. Conclusion

Perfusion CT can offer both morphologic and functional information, providing a quantitative assessment of residual tumor vascularization after chemotherapy and radio-therapy, first-pass whole nodule perfusion imaging is a technically feasible tool to assess the haemodynamics of pulmonary nodules. Perfusion parameters offer utility in distinguishing benign nodules from malignant tumors. Absence of perfusion and relatively low blood volume are strong predictors that the pulmonary nodule is benign. CT perfusion is a feasible non-invasive diagnostic technique able to evaluate treatment response in patients with metastatic pulmonary nodules.

Abbreviations

CT: Computed Tomography; EF: Extraction Fraction; FDG: Fluorodeoxy-glucose; MDCT: Multi-detector row CT; MR: Magnetic Resonance; PET: Positron Emission Tomography; PF: Perfusion Flow; PV: Blood Volume; REC: Research Ethics Committee; ROIs: Region of Interests; TDc: Time Density Curve.

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