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Original Article

CT Perfusion Study in Pulmonary Masses

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Purpose : To compare the Computed Tomography (CT) perfusion parameters involving malignant and benign lung lesions and of various histological types of malignant lung neoplasms.

Materials and Methods : Perfusion parameters ie Blood Flow (BF), Blood Volume (BV), Mean Permeability Surface Area Product (PS), Time to peak (TTP) and Mean Transit Time (MTT) underwent analysis. Each mean value with the 95% Confidence Interval (CI) was obtained. A "p" value of <0.05 indicates statistical significance.

Results : The mean value (lower CI- Upper CI) of BF, BV,PS, TTP and MTT in benign and malignant lesions was calculated. Similarly, the mean value with CI for each parameter was obtained for adeno carcinoma, squamous cell carcinoma, small cell carcinoma(SCC), large cell carcinoma (LCC) and metastases individually.

Conclusion : Statistically significant difference was noted between benign and malignant lesions based on BF, BV and PS. Statistically significant difference was noted between all subtypes on BV with the exception of adeno carcinoma versus SCC. BF also showed statistically significant difference between all subtypes with the exception of Squamous cell carcinoma versus LCC and SCC versus metastases.

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Key words **: CT perfusion, Blood Volume, Blood Flow, Mean Transit Time, Lung cancer.**

Lung cancer is the most common cause of cancer related death in the world, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of total number). It is the most common cancer among men with highest estimated age standardized incidence in central, Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000)[1]. Pathologically lung cancer is broadly divided into small-cell lung cancer (SCC, comprising 20% of lung cancers), and non-small-cell lung cancer (NSCLC, comprising 80% of lung cancers). SCC is a tumour of neural crest origin. NSCLC is thought to originate in lung epithelial cells and comprises diverse histological subtypes including adenocarcinoma, squamous, anaplastic and large-cell carcinomas[2].

Lung cancer presents as an incidentally detected pulmonary nodule /mass in 30-40% of cases. Distinguishing malignant and benign nodules using conventional radiography and computed tomography is a major diagnostic challenge and a large percentage of lesions show overlapping features. Since benign and malignant neoplasms differ in patterns of angiogenesis, a functional imaging modality which can reflect perfusion patterns of pulmonary nodules can be very helpful in differentiating them.

Editor's Comment :

- CT perfusion study can be taken as an important adjunct tool for characterization of pulmonary masses.
- It was observed in our study that BF, BV and PS showed statistically significant difference between benign and malignant lesions.
- BF and BV showed statistically significant difference between the most number of subtypes of malignant lesions.

Perfusion is the supply of blood to a unit volume of tissue per unit of time and usually at the capillary level. Tissue enhancement over time represents the rate and amount of contrast material distribution in the vascular space and extravascular, extracellular space. By using various mathematical models adjusted to the arterial attenuation, measurement of tissue attenuation over time can describe physiologic parameters like blood volume, blood flow rate, tissue permeability, and mean transit time. Perfusion values have shown significant differences when comparing normal tissue versus tumours and malignant versus benign lesions within the lung, liver, pancreas and bowel. In general, higher perfusion parameters were reported in patients with brain, hepatic, rectal, lung, gastric, head and neck and neuroendocrine tumours, although the angiogenic phenotype is diverse between different type of tumours and also in the same type of tumour[3].

Primary objective of the study is Comparison of

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Computed Tomography (CT) perfusion parameters of malignant versus benign lung lesions. Secondary objective of the study is comparison of CT perfusion parameters characterising various histological types of malignant neoplasms of the lung. Perfusion parameters used for comparison are : (1) Blood flow (BF) which means the volume flow rate of blood through the vasculature (expressed as mL/min/100 mL) (2) Blood volume (BV) ie, the volume of blood within the vasculature that is really flowing (expressed in units of mL/100mL) (3) Mean transit time (MTT) ie, average time it takes for blood to transport between the arterial inflow and venous outflow, measured in seconds (4) Permeability surface area product (PS) ie, the product of permeability and total surface area of capillary endothelium in a unit mass of tissue or tumour (measured as mL/min/100 mL) (5) Time to Peak (TTP) ie, the time at which contrast concentration reaches its maximum, in seconds.

Materials and Methods

The prospective observational study was conducted at the Department of Radiodiagnosis of Medical Trust Hospital from August, 2016 till September, 2017 after taking consent from patients and approval by the Ethics Committee. It was done to observe the characteristics of lung lesions on CT perfusion study and how the perfusion parameters differ among benign and malignant lung pathologies and also among the various histological subtypes of the malignant masses. The source of data was patients who were referred to our Department of Radiodiagnosis, for contrast Enhanced CT (CECT) thorax for evaluating pulmonary lesions. Based on the previous study[4] it was observed that the proportion of patients who have large cell carcinoma was 7.1%, precision was 8% and with 95% Confidence Interval, the minimum required sample size was found to be 40. We used here the software nMaster 2.0 and the following formula has been used for sample size calculation.

Formula

$N= z^2(1-\alpha/2)\ p(1-p)/r^2$

Where,

p : Expected proportion = 0.071

r : Absolute precision = 8

1- $\alpha/2$: Desired Confidence level=95%

N=40

Calculation

Sample size $n= [1.96^2 *0.071(1-0.071)]/\{.8\}^2=40$.

Inclusion Criteria :

Patients diagnosed with pulmonary lesions in chest Xray, who were referred for contrast CT thorax, were included in this study. Following inclusion criteria were used.

- All lesions were larger than 10mm which had no areas of fat, calcification or necrosis.
- Who did not undergo any chemotherapy or radiotherapy.
- Age more than 40 years, in view of increased radiation dose.

Exclusion Criteria

- Subjects of reproductive potential, who are sexually active but unwilling and/or unable to use medically appropriate contraception, or women who are pregnant or breastfeeding.
- Documented allergy to iodinated contrast media.
- The patient should not have any renal compromise with creatinine being less than 1.5 mg/dl and/or estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m^2.

Data Acquisition :

After obtaining informed consent from patients who satisfied the inclusion and exclusion.

criteria CT perfusion was performed using a 128-detector row dual energy CT scanner [General Electric (GE) Revolution, France]. A 19-gauge cannula was inserted into antecubital vein prior to the examination.

A bolus of 50 ml of iodinated low-osmolar non-ionic contrast material (Ultravist 300, Schering, Berlin Germany) was injected intravenously at the rate of 4-5 ml/sec using a pump injector (The Salient™ CT Injector, Bayer, NSW, Australia). After acquiring non-contrast High Resolution CT (HRCT) thorax, dynamic acquisitions encompassing the entire nodule (20 shuttle passes) were done around 5 s following the start of bolus injection using the following parameters:

120 kV; 80mAs; rotation time, 0.50 s; table speed 110 mm/s; detector coverage, 40.0 mm; helical thickness,5mm; field of view, 350 mm; matrix, 512X 512. Total duration time was different for various patients but was approximately 34s (30-40s). Accumulated average exam dose length product was 1639.98 mGy-cm.

Following completion of CT examination, data was transferred to a stand-alone workstation (GE Advantage 4.6) and analyzed with a commercial CT perfusion software (CT perfusion 4D).

The artery input was calculated after placing a circular region of interest (ROI) over the aorta or the left subclavian artery in case the aorta was not included in the section. Perfusion parameters of the nodule were calculated on a circular or oval ROI around the

peripheral region of lesion avoiding lung tissue with atelectasis and cavitation. The analytical method that was used in this study was based on the deconvolution model. Five major kinetic parameters were obtained (1) BV measured as ml/100ml (2) BF measured as ml/min/100ml (3) MTT measured as sec (4) PS measured as ml/min/100ml (5) TTP measured in sec. Colour parametric and composite maps of these perfusion parameters were spontaneously generated and recorded .

All lesions were biopsied under CT guidance by a senior radiologist with over 10 years of experience and histological diagnosis was made. Lesions were categorised into two groups namely malignant and benign.

Further, the malignant variety was subdivided into adeno carcinoma , squamous cell carcinoma, small cell SCC, large cell carcinoma (LCC) and metastases based on histology.

Perfusion parameters of each group were analyzed using a statistical software named International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) ver.20 to find out significant difference among various groups. Normality was checked by Kolmogrov-Smirnove test.

For independent samples Kruskal-Wallis H test was used for testing the significance among the non-parametric data. The mean and 95% confidence interval (CI) was calculated for all parameters .Pearson Chi-square test, fisher's exact test was utilised to find the relation between categorical variables. A p-value of <0.05 was taken to be statistically significant.

Results

40 patients (29 men and 11 women) with a mean age of 63 years, who satisfied the inclusion and exclusion criteria were included and taken up for CT Perfusion study. Table 1 demonstrates the sex distribution of the population. Some of the representative cases have been reported in detail, in the following section, along with their respective images.

Case Examples :

Fig 1 (1a,1b and 1c) shows the CT perfusion images of a 40-year-old male who had a lesion measuring 3 x 3cm on chest Xray. Post processing analysis of images using CT perfusion software showed following values, BF-194ml/min/100ml, BV-10ml/100ml, MTT-3.6sec and PS-27 ml/min/100ml. High perfusion parameters suggested the possibility of malignancy. A CT guided biopsy was taken from the lesion. This was proved to be adenocarcinoma histologically.

Fig 2 (2a,2b,2c,2d) shows the CT perfusion images of a 78-year-old male who had a lesion measuring 3.2 x 3cm on chest Xray. Post processing analysis of images using CT perfusion software showed following values, BV-26 ml/100ml, BF-206ml/min/100ml, MTT-2.3 sec, PS-3.8ml/min/100ml, TTP-5.8sec. High perfusion parameters suggested the possibility of malignancy. A CT guided biopsy was taken from the lesion. This was proved to be squamous cell carcinoma

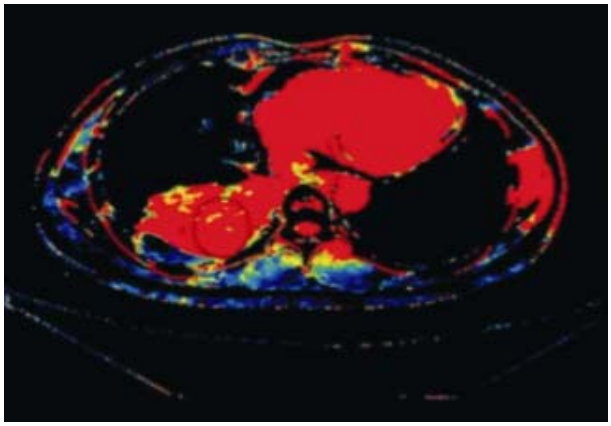

Fig 1a — Axial CT of thorax with perfusion map placed over mass in right lower lobe showing BF= 194ml/min/100ml

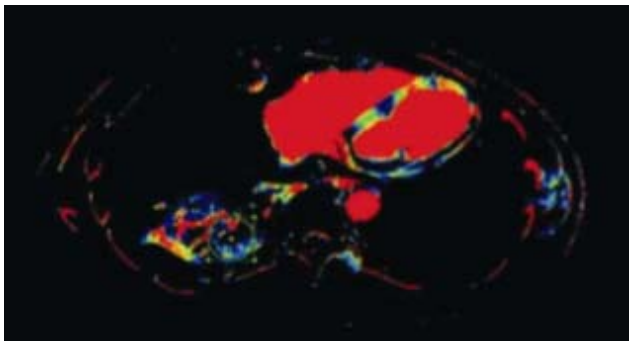

Fig 1b — Axial CT of thorax with perfusion map placed over mass in right lower lobe perfusion map showing BV=10 ml/100ml

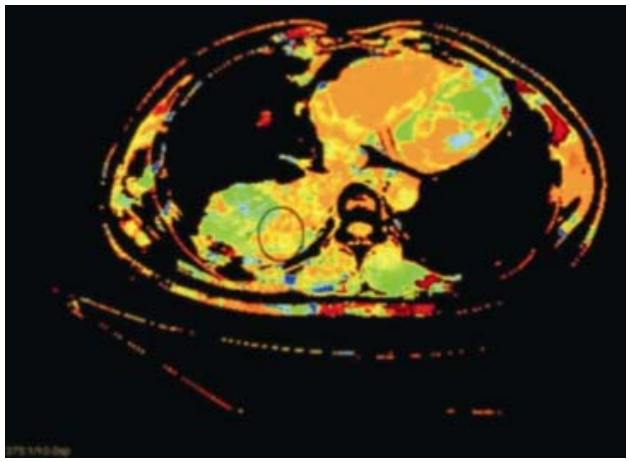

Fig 1c — Axial CT of thorax with perfusion map placed over mass in right lower lobe perfusion map showing MTT = 3.6 sec

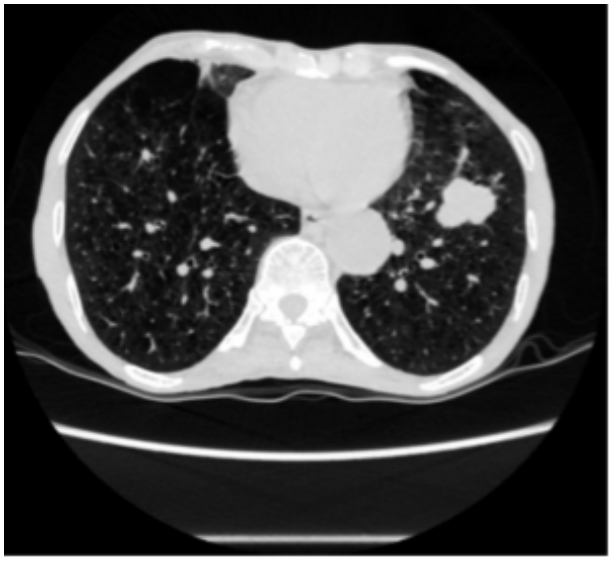

Fig 2a — Axial CT of thorax showing a mass with lobulated margins in left upper lobe

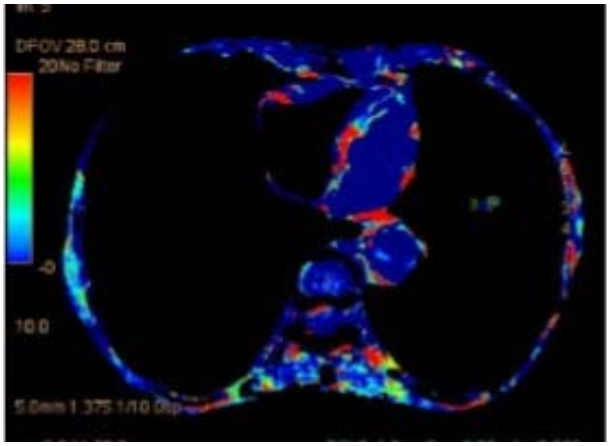

Fig 2b — Axial CT of thorax with perfusion map placed over mass in left upper lobe showing PS=3.8ml/min/100ml

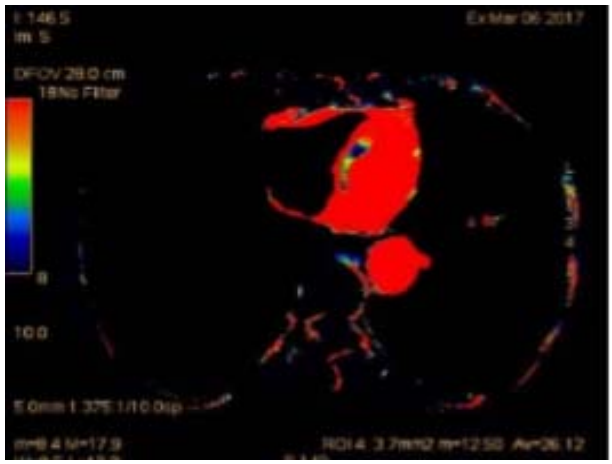

Fig 2c — Axial CT of thorax with perfusion map placed over mass in left upper lobe showing BV= 26ml/100ml

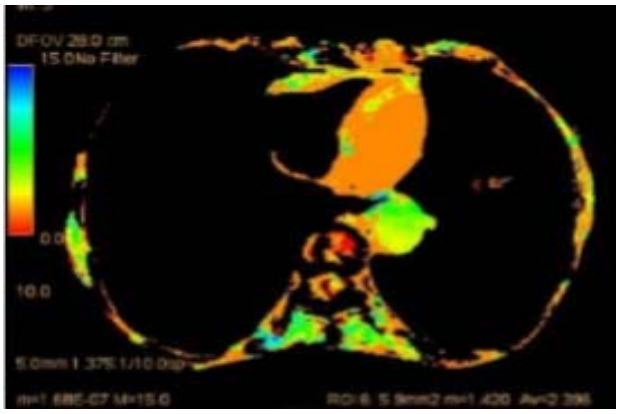

Fig 2d — Axial CT of thorax with perfusion map placed over mass in left upper lobe showing MTT=2.3 secs

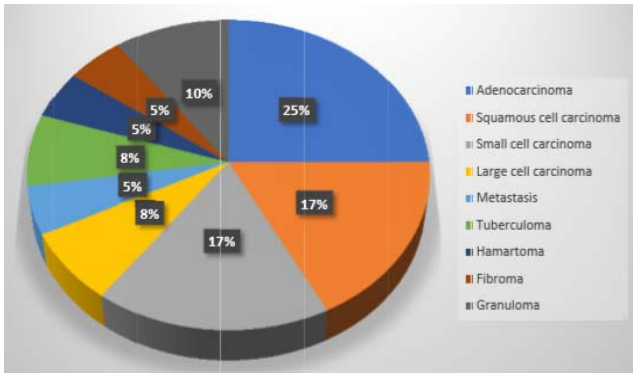

Fig. 3 — Pie chart showing histological distribution of all cases both benign and malignant

histologically.

Among 29 patients with malignancies – 10 had adenocarcinoma, 7 had squamous cell and small cell varieties each, 3 had large cell variety and 2 had metastases. The rest of the 11 patients had benign lesions which included 3 patients with tuberculoma, 2 with hamartoma, 2 with fibroma and 4 had granuloma. Fig 3 is a pie chart showing the distribution of all the lesions (benign and malignant).

Table 2 shows correlation among the various perfusion parameters. Positive correlation was found between BF with BV(r=0.566) and BF with PS (r=0.512). Negative correlation was found between BF and MTT(r=-0.225).Positive correlation was seen between BV with PS (r=0.644) and BV with BF (r=0.512).Negative correlation was seen between BV and MTT (r=- 0.836).Positive correlation was found between MTT with BV (r=0.644). Negative correlation was seen between PS and MTT (r=-0.109). Positive correlation was seen between TTP with MTT (r=0.153). Negative correlation was observed between TTP with BV (r= -0.215), TTP with BF (r=-0.299) and TTP with PS (r= -0.258).

Table 1 — *Demonstrates the sex distribution of the population*

Sex	Number	Percentage
Male	29	72
Female	11	28

Table 2 — *Correlation among the various perfusion parameters*

Correlation	Pearson Correlation Value	Type of Correlation
BF Vs BV	0.566	Positive
BF Vs PS	0.512	Positive
BV Vs PS	0.644	Positive
MTT Vs BV	0.644	Positive
BF Vs MTT	-0.225	Negative
BV Vs MTT	-0.036	Negative
PS Vs MTT	-0.109	Negative
BV vs TTP	-0.215	Negative
BF vs TTP	-0.299	Negative
MTT vs TTP	0.153	Positive
PS vs TTP	-0.258	Negative

Table 3 — *Comparison between benign and malignant lesions based on BF*

Type	Mean (ml/min/100ml) (Lower CI- Upper CI)	P value
Benign	55.0 (42.6-67.4)	0.018
Malignant	167.4 (121.5- 213.3)	

Table 4 — *Comparison between benign and malignant lesions based on BV*

Type	Mean (ml/100ml) (Lower CI- Upper CI)	P value
Benign	7.5 (4.5 -10.5)	0.024
Malignant	18.1 (15.0-21.2)	

Table 5 — *Comparison between benign and malignant lesions based on MTT*

Type	Mean (seconds) (Lower CI-Upper CI)	P value
Benign	9.9 (5.2-14.6)	0.577
Malignant	8.6 (6.5-10.7)	

Table 6 — *Comparison between benign and malignant lesions based on PS*

Type	Mean (ml/min/100ml) (lower CI-upper CI)	P value
Benign	12.0 (7.3-16.7)	0.003
Malignant	22.0 (18.9-25.1)	

Table 7 — *Comparison between benign and malignant lesions based on TTP*

Type	Mean (seconds) (Lower CI- Upper CI)	P value
Benign	16.3 (10.0-22.7)	0.064
Malignant	18.2 (14.6-21.9)	

Table 3 compares the benign and malignant lesions based on BF. Statistically significant difference was observed between malignant and benign lesions ($p<0.05$). The mean value (lower CI-upper CI) of BF was 55.0 (42.6-67.4) and 167.4 (121.5- 213.3) ml/min/100ml respectively.

Table 4 shows the comparison between benign and malignant lesions based on BV. Statistically significant difference was noted between benign and malignant lesions ($p<0.05$). The mean value(lower CI-upper CI) of BV was 7.5 (4.5 -10.5) and 18.1 (15.0-21.2) ml/100ml respectively.

Table 5 shows the comparison between benign and malignant lesions based on MTT. No statistically significant difference was observed between malignant and benign lesions($p>0.05$). The mean value of MTT (lower CI-upper CI) was 9.9 (5.2-14.6) and 8.6 (6.5-10.7) seconds respectively.

Table 6 shows the comparison between benign and malignant lesions based on PS. Statistically significant difference was noted between benign and malignant lesions ($p<0.05$). The mean value of PS (lower CI-upper CI) was 12.0 (7.3-16.7) and 22.0 (18.9-25.1) ml/min/100ml respectively.

Table 7 shows the comparison between benign and malignant lesions based on TTP. No statistically significant difference was noted between benign and malignant lesions ($p>0.05$). The mean value of TTP (lower CI-upper CI) was 16.3 (10.0-22.7) and 18.2 (14.6-21.9) seconds respectively.

Table 8 shows the mean values of the different perfusion parameters among the different subtypes of malignancy with the CI. BV and BF showed difference in value among majority of the subtypes.

Table 9 shows the p values comparing the different subtypes of malignancy based on each perfusion parameter separately. BV and BF showed statistically significant difference among the majority of different types of malignancies ($p<0.05$). Other parameters (MTT, TTP and PS) showed statistically significant difference between few subtypes.

Discussion

Only a few studies have been described in literature which used CT perfusion for characterization of pulmonary lesions and most of them did not compare the different histological subtypes of malignancy. Our study not only tries to differentiate benign versus malignant etiology based on perfusion, but also attempts to categorise the various histological varieties of malignancy. In 2008 Sitartchouk et al showed that perfusion parameters viz MTT,BF and PS showed statistically significant difference in benign and malignant nodules[5]. In our study also similar results were obtained except for MTT which did not show statistically significant difference. Roberts H *et al*[6] showed that PS value can differentiate benign from malignant nodules akin to our results. In 2007 Ruan CM *et al*[7] proved that the values of BF and BV were significantly higher in malignant masses, but MTT did not show any difference. The study by Ohno Y *et al*[4], comparing the capability of CT perfusion with combined

Table 8 — *Mean value of the perfusion parameters among the different subtypes of malignancy with the CI*

Histological Type	Mean value (Lower CI-Upper CI)
Blood Volume (ml/100ml) :	
Adenocarcinoma	13.7(8.6-18.8)
Squamous Cell carcinoma	23.0(16.1-30)
Small Cell Carcinoma	13.4(3.6-23.3)
Large Cell Carcinoma	26.8(18.4-35.1)
Metastasis	17.5((10.2-24.2)
Blood Flow (ml/min/100ml) :	
Adenocarcinoma	86.6(59.9-113.2)
Squamous Cell carcinoma	269.6(133.9-405.3)
Small Cell Carcinoma	118.9(47.5-190.2)
Large Cell Carcinoma	209.6(73.4-345.7)
Metastasis	117(80.0-144)
Mean Transit Time (seconds) :	
Adenocarcinoma	8.3(4.4-12.3)
Squamous Cell carcinoma	4.4(2.0-6.7)
Small Cell Carcinoma	8.2(3.7-12.8)
Large Cell Carcinoma	15.3(9.0-21.5)
Metastasis	16.1(10.0-22.1)
Time to Peak (seconds) :	
Adenocarcinoma	15.8(7.7-23.9)
Squamous Cell carcinoma	11.1(4.2-18.0)
Small Cell Carcinoma	23.9(18.5-29.3)
Large Cell Carcinoma	20.1(10.2-30.3)
Metastasis	17.6(5.5-29.7)
Mean Permeability Surface area product (ml/min/100ml) :	
Adenocarcinoma	20.3(14.2-26.5)
Squamous Cell carcinoma	27.1(22.7-31.5)
Small Cell Carcinoma	20.7(8.0-33.4)
Large Cell Carcinoma	20.8(11.3-30.3)
Metastasis	21.8(11.2-33.2)

positron emission tomography and CT (PET/CT) found that all results in the malignant nodule group were significantly different from that in the benign nodule group (P <0.05). Venkat *et al*[8], performed CT perfusion in eighty five patients and found strong positive correlation of BF with BV and BF with PS , and weak positive correlation between BV and MTT. They obtained higher values of BV, BF and MTT in adenocarcinoma when compared to other histological subtypes. In our study, we found significant positive correlation between BF and BV, BF and PS, MTT and BV. Further, BF and BV showed statistically significant difference between the majority of the histological varieties of malignancy. In 2016 LV *et al*[9] found that the perfusion parameters of BV, MTT, BF and PS in the lung cancer group showed significantly higher values than those in the non-cancer group.In our study also similar results were obtained except for MTT.In 2018, Hou *et al*[10],showed that levels of MTT, PS, BV

Table 9 — *P values comparing the different subtypes of malignancy based on each perfusion parameter separately*

Diagnosis	P value
BV (ml/100ml) :	
Adenocarcinoma v Squamous cell carcinoma	0.04
Adenocarcinoma v SCC	0.07
Adenocarcinoma v LCC	0.04
Adenocarcinoma v metastases	0.04
Squamous cell carcinoma v SCC	0.04
Squamous cell carcinoma v LCC	0.04
Squamous cell carcinoma v metastases	0.03
SCC v LCC	0.04
SCC v metastases	0.03
LCC v metastases	0.04
MTT (seconds) :	
Adenocarcinoma v Squamous cell carcinoma	0.04
Adenocarcinoma v SCC	0.06
Adenocarcinoma v LCC	0.06
Adenocarcinoma v metastases	0.04
Squamous cell carcinoma v SCC	0.03
Squamous cell carcinoma v LCC	0.06
Squamous cell carcinoma v metastases	0.04
SCC v LCC	0.035
SCC v metastases	0.04
LCC v metastases	0.06
BF(ml/min/100ml) :	
Adenocarcinoma v Squamous cell carcinoma	0.04
Adenocarcinoma v SCC	0.035
Adenocarcinoma v LCC	0.04
Adenocarcinoma v metastases	0.04
Squamous cell carcinoma v SCC	0.04
Squamous cell carcinoma v LCC	0.055
Squamous cell carcinoma v metastases	0.04
SCC v LCC	0.045
SCC v metastases	0.07
LCC v metastases	0.045
Time to peak(seconds) :	
Adenocarcinoma v Squamous cell carcinoma	0.055
Adenocarcinoma v SCC	0.04
Adenocarcinoma v LCC	0.04
Adenocarcinoma v metastases	0.07
Squamous cell carcinoma v SCC	0.04
Squamous cell carcinoma v LCC	0.045
Squamous cell carcinoma v metastases	0.055
SCC v LCC	0.06
SCC v metastases	0.045
LCC v metastases	0.055
PS(ml/min/100ml) :	
Adenocarcinoma v Squamous cell carcinoma	0.055
Adenocarcinoma v SCC	0.06
Adenocarcinoma v LCC	0.06
Adenocarcinoma v metastases	0.06
Squamous cell carcinoma v SCC	0.045
Squamous cell carcinoma v LCC	0.04
Squamous cell carcinoma v metastases	0.045
SCC v LCC	0.07
SCC v metastases	0.08
LCC v metastases	0.07

and BF significantly increased with malignant Solitary Pulmonary Nodules (SPN)s compared to benign. Shan *et al*[11] in 2012 showed using threshold of BV,BF and PS values of more than 55 ml/100 g/min, 2.5 ml/100 g, and 10 ml/100 g/min respectively, SPNs were more likely to be malignant. In 2010, Y Li *et al*[12] proved that BF, and BV for malignant nodules was significantly higher than benign SPNs. Ma *et al*[13] showed significant difference of malignant and benign nodules using BF,BV and PS. Data from Wang *et al*[14],showed BF, BV, MTT, and PS values in benign SPN group was significantly lower than malignant.Our study showed statistically significant difference between benign and malignant lesions using BF, BV and PS.The main limitation of our study was the relatively small sample size and we did not include the pre treatment and post treatment change in perfusion parameters in our study design.

However, based on our results, we recommend use of CT perfusion to reliably differentiate benign and malignant lung lesions based on particular parameters. Further BV, BF can also differentiate between different histological subtypes of malignant lung cancer to a great extent. In appropriate cases this utility can be used as an additional tool to routine imaging evaluation for rapid diagnosis of lung cancer.

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Conflict of Interest : None

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