Computed tomography perfusion (CTP) in primary lung cancer: Results from a tertiary care centre

Mafeed Arimbrakkunnan¹, Pawan K. Garg¹, Pushpinder S. Khera¹, Binit Sureka¹, Poonam Elhence², Puneet Pareek², Nishant Kumar Chauhan³, Taruna Yadav¹

¹Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India, ²Department of Pathology and Lab Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India, ³Department of Radiation Oncology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

ABSTRACT

Context: Lung cancer is the leading cause of cancer-related deaths in the world. Computed tomography perfusion (CTP) parameters can be used to evaluate the vascular flow dynamics of lung tumours. We set out to evaluate the CTP parameters in lung cancer and correlate them with histopathological subtype and other characteristics of patients with Lung Cancer. Settings and Design: This prospective study was conducted at a tertiary care referral hospital in western India. Methods: Between January 2019 and July 2020, CTP was performed in 46 patients of lung cancer with histopathological confirmation. The CTP parameters were evaluated in detail and correlated with histopathological subtypes, staging and immunohistochemistry (IHC) markers. Analysis of variance (ANOVA) test, receiver operator characteristic (ROC) curve, Box and whiskers plot graph and Pearson correlation tests were used for statistical analysis. Results: The most common subtype was adenocarcinoma (AC) in 21 patients, followed by squamous cell carcinoma (SCC) in 15 patients and others in 10 patients. Statistically significant difference in blood flow (BF) (f = 5.563, P = 0.007), blood volume (BV) (f = 3.548, P = 0.038) and permeability/flow extraction (FE) (f = 3.617, P = 0.036) were seen in different histopathological subtypes of lung cancer. BF is the main perfusion parameter for differentiation of AC from SCC. P63 positive lesions showed statistically significant lower BF, BV and FE parameters compared to P63 negative lesions (P = 0.013, 0.016 and 0.014, respectively). Different T stages showed statistically significant differences in BF (f = 3.573, P = 0.037), BV (f = 5.145, P = 0.010) and in FE (f = 4.849, P = 0.013). Conclusion: CTP is a non-invasive imaging method to assess the vascular flow dynamics of the tumours that may predict the histopathological subtypes in lung cancer. It can be used to target large-sized lesions during biopsy and to predict the chemotherapy response.

KEY WORDS: Blood flow (BF), blood volume (BV), computed tomography perfusion (CTP), FE – flow extraction product, lung cancer, mean transit time (MTT), permeability

Address for correspondence: Dr. Pawan K. Garg, Associate Professor, Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences, Jodhpur - 342 005, Rajasthan, India.
E-mail: drgargpawan@gmail.com

Submitted: 22-Jun-2021 Accepted: 03-Mar-2022 Published: 20-Apr-2022
INTRODUCTION

Despite improvements in diagnostic and therapeutic modalities, lung cancer stands among the leading cause of cancer-related death in the world. As per the 2018 Global Cancer Observatory (GLOBOCAN) report, lung cancer affected around 2.1 million people (11.6% of all cancers) worldwide and resulted in 1.8 million deaths (accounting for 18.4% of cancer-related mortality). The high burden of disease and attributable mortality makes lung carcinoma an important public health problem.

Various imaging modalities are being used for the detection, characterisation, staging and follow-up of lung cancer. Chest radiography is the initial investigation wherein lung tumours are seen as nodules or masses with irregular-spiculated margins, or focal areas of consolidation. The drawbacks of radiography include technical errors and failure of detection of smaller lesions in hidden areas such as apices, retrocardiac and perihilar regions. Contrast-enhanced computed tomography (CECT) is the imaging modality of choice in lung cancer evaluation and staging. Computed tomography (CT) is useful in assessing tumour size and depicts mediastinal invasion, size of the mediastinal lymph nodes, pleural effusion and distant metastasis. However, for parietal pleural involvement, transthoracic ultrasound and MRI give better results.

Perfusion studies assess tumoral microcirculation and angiogenesis properties. Among perfusion imaging techniques, single-photon emission computed tomography (SPECT), positron emission tomography (PET) and dynamic contrast-enhanced magnetic resonance imaging (CE-MRI) have utility for the same. Computed tomography perfusion (CTP) is an emerging technology assessing tissue vascularity through various perfusion parameters.

The earliest body CTP parameters were reported in 1993 by Miles et al. They quantified the arterial and portal components of hepatic perfusion separately. Initially, CTP evaluation was limited due to short Z-axis coverage, poor reproducibility and cumbersome post-processing. Rapid technological advancements in CT scanners provide longer coverage and helical mode acquisition, covering the entire tumoral volume in a short time span. Commercial software workstations made CTP post-processing and evaluation less cumbersome and consistent.

The significant impact of CTP is in the assessment of acute stroke patients and treatment decisions. The other area where CTP is of value is in oncologic imaging, for tumour diagnosis, staging, prognostication and post-treatment response. The functional parameters obtained by CTP are blood flow (BF), blood volume (BV), mean transit time (MTT) and permeability (denoted as K-trans/FE – flow extraction product) and represent oncological markers of the tumour.

Our study aimed to evaluate the CTP parameters in lung cancer and study their correlation with histopathological subtype and other characteristics of the tumour.

MATERIALS AND METHODS

After approval from the institutional ethical committee, patients with suspected malignant lung lesions on any imaging modality were enrolled in the study. CTP of the lung lesion was performed using Siemens, SOMATOM Definition Flash Dual Source Dual Energy 128 × 2 slice CT scanner. Lesion localisation and Z-axis coverage (10 cm) determination were done on the topogram. In cases where the lesion was not well defined on topogram, a non-contrast CT was acquired at 80 kV for the same. Further, 45 mL of iodinated contrast agent (Iohexol, 350 mgI/mL) was injected from the right antecubital vein at 5 mL/s, followed by a 30-mL saline bolus chase to minimise streak artifacts. Twenty-seven scans were acquired in helical shuttle mode over 41.7 s after a 2-s delay of contrast injection initiation. Images were acquired at 80 kV and 50–100 mA with automated tube current modulation, rotation time of 0.28 s, 5.0-mm slice thickness initially and later reconstructed at 3.0-mm thickness. CECT of the chest and upper abdomen was done in those patients who had not undergone a staging CT previously.

Post-processing was done on Siemens Advanced MM workstation Syngo Via VB 30 platform. Computerised alignment and motion correction was done automatically by the software. Aorta and its branches were used to place the region of interest for arterial comparison. The display of perfusion maps included soft tissue and mediastinum and excluded bones and calcifications. Colour-coded maps for perfusion parameters were generated using the inbuilt software in the workstation. Source images, perfusion maps and other parameter values were reviewed by two radiologists, MAK and PG with an experience of 3 and 8 years, respectively, and the consensus was agreed upon.

The program estimated tissue perfusion by the deconvolution method. Tabulated data of perfusion parameters (BF, BV, MTT and FE) were obtained using the freehand technique by drawing the volume of interest (VOI) along the lesion. Necrotic areas, vessels, calcifications and atelectatic lung were identified on unprocessed source images and excluded from selecting VOI. TNM staging and stage grouping were done according to the 8th edition of the American Joint Committee on Cancer (AJCC)-approved staging classification.

All patients underwent ultrasound, CT or bronchoscopy-guided sampling of the lesion as part of the standard protocol. The pathologists analysed and classified the tumours based on the World Health Organisation (WHO) histological classification of lung malignancy, and the report was considered as outcome reference.
Table 1: Various perfusion parameters, their definition and their physiological surrogate in oncology

| Perfusion parameter (Unit)                      | Definition                                   | Marker (In Oncology)                  |
|------------------------------------------------|----------------------------------------------|---------------------------------------|
| BF-Blood Flow (mL/100 g/min)                   | Flow rate through the vasculature in the tissue region | Tumor vascularity, Tumor grade       |
| BV-Blood volume (mL/100 g)                     | Volume of flowing blood within a vasculature in the tissue region | Mitotic activity and vascularity      |
| MTT-Mean transit time (Seconds)                | Average time taken to travel from artery to vein | Perfusion pressure                    |
| FE-Permeability/Flow extraction product (mL/100 g/min) | Total flux from plasma to interstitial space | Immature leaky vessels                |

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 23.0 (Armonk, NY: IBM Corp.). Qualitative variables such as age, gender, clinical symptoms, histological subtypes and stage of the lesions were described by frequency and percentages. Perfusion parameters were considered as continuous variables, and mean, median, standard deviation and standard errors were calculated from the data. Analysis of variance (ANOVA) was applied on each perfusion parameter obtained from CTP, different histological subtypes and different TNM stages. A Tukey post-hoc test was used to identify the pairwise average mean differences of perfusion parameters between the subtypes. Diagnostic accuracy was assessed using the receiver operator characteristic (ROC) curve, and the cut-off to differentiate AC from non-adenomatous lung cancer was estimated. Results with $P<0.05$ were regarded as statistically significant. Pearson correlation test was used for determining the degree of association between two variables.

RESULTS

From January 2019 to July 2020, 53 consecutive patients with suspected lung malignancy who fulfilled the inclusion criteria were recruited. Two patients with suboptimal images and five patients with benign disease on CT or histopathology were excluded. Thus, a total of 46 patients with CTP evaluation and histopathologically proven lung malignancy constituted the final study population.

Forty-six patients [39 males (84.78%) and seven females (15.22%)] were included in the study with a mean age of 61.4 $\pm$ 9.57 years (range: 45–84 years). Out of these, 31 (67.39%) had a smoking history. Weight loss and cough constituted the most common clinical symptoms, seen in 42 (91.30%) and 36 (78.26%) patients, respectively. Other symptoms included chest pain, shortness of breath and haemoptysis. Seventeen patients had symptoms such as back pain, seizure and hemiparesis due to secondary metastasis. Twenty-five patients had metastasis (54.34%) belonging to stage IVA and IVB disease. Other patients had locally advanced tumours belonging to stage III. No stage I or II lesions were seen [Table 2].

Twenty-one patients (45.65%) had AC [Figure 1], constituting the major subtype, followed by SCC in 15 patients (32.60%) [Figure 2]. Ten patients (21.74%) had other variants of lung carcinoma, including poorly differentiated carcinoma (PDC), adeno-squamous cell carcinoma (ASC) and small cell lung carcinoma (SCLC).

Table 2: General characteristics of the study population (Total 46 patients)

| Characteristic                        | Number (percentage) |
|---------------------------------------|---------------------|
| Gender                                |                     |
| Male                                  | 39 (84.78)          |
| Female                                | 7 (15.22)           |
| Smoking exposure                      |                     |
| Yes                                   | 31 (67.39)          |
| No                                    | 15 (32.61)          |
| Clinical symptoms                     |                     |
| Weight loss                           | 42 (91.30)          |
| Cough                                 | 36 (78.26)          |
| Chest pain                            | 24 (52.17)          |
| Shortness of breath (SOB)             | 24 (52.17)          |
| Hemoptysis                            | 9 (19.56)           |
| Symptoms of secondaries               | 17 (36.95)          |
| Histopathological subtype             |                     |
| Adenocarcinoma (AC)                   | 21 (45.65)          |
| Squamous cell carcinoma (SCC)         | 15 (32.60)          |
| Others                                |                     |
| Poorly differentiated carcinoma (PDC) | 7 (15.21)           |
| Adenosquamous cell carcinoma (ASC)    | 2 (4.34)            |
| Small cell lung carcinoma (SCLC)      | 1 (2.17)            |
| TNM staging                           |                     |
| IVA B                                 | 16 (34.78)          |
| IV A                                  | 9 (19.56)           |
| III C                                 | 2 (4.34)            |
| III B                                 | 15 (32.61)          |
| III A                                 | 4 (8.69)            |

Initial evaluation of perfusion parameters in different lung cancer subtypes [AC, SCC and others (including PDC, SCLC and ASC)] by using one-way ANOVA test showed no statistically significant results ($P>0.05$) [N = 46]. However, on analysing the values, we noted that two lesions (ID14 and ID40) had very low perfusion values (BF $<20$ mL/100 g/min), causing skewness of the data and negatively affecting the study’s statistical significance [Figure 3]. Inspired by Bevilacqua et al., [13] we excluded these two cases, which revealed statistically significant differences in BF ($f = 5.563$, $P = 0.007$), BV ($f = 3.548$, $P = 0.038$) and FE ($f = 3.617$, $P = 0.036$) in different lung carcinoma subtypes [N = 44] [Table 3]. MTT did not show any statistically significant differences between the subtypes. Box and whiskers plot graph showed BF as the chief perfusion parameter in differentiating AC from SCC [Figure 4].

Correlation of perfusion parameters to IHC markers (TTF-1 and P63) was done in available cases (27 and 23, respectively). P63 positive lesions showed statistically significant lower perfusion (BF, BV and FE) compared to P63 negative lesions ($P = 0.013$, 0.016 and 0.014, respectively) [Table 4]. No statistically significant differences were obtained for the TTF-1 status of lesions,
though the BF, BV and FE were higher in TTF-1-positive lesions. Different T stages showed statistically significant differences in BF ($F = 3.573, P = 0.037$), BV ($F = 5.145,$
Arimbrakkunnan, et al.: Computed tomography perfusion in primary lung cancer

Table 4: CT Perfusion parameters and IHC marker analysis - (Results by independent samples t-test)

| P63 status                        | Numbers | Mean   | SD    | SE   | Sig (2-tailed) |
|-----------------------------------|---------|--------|-------|------|----------------|
| Blood Flow - BF (mL/100 g/min)    |         |        |       |      |                |
| Negative                          | 12      | 71.1   | 21.1  | 6.1  | 0.013*         |
| Positive                          | 11      | 48.6   | 18.1  | 5.4  |                |
| Blood volume-BV (mL/100 g)       |         |        |       |      |                |
| Negative                          | 12      | 5.7    | 1.9   | 0.55 | 0.016*         |
| Positive                          | 11      | 3.8    | 1.4   | 0.43 |                |
| Mean transit time- MTT (s)        |         |        |       |      |                |
| Negative                          | 12      | 5.4    | 0.9   | 0.28 | 0.542          |
| Positive                          | 11      | 5.2    | 0.5   | 0.17 |                |
| Permeability/Flow extraction- FE (mL/100 g/min) |         |        |       |      |                |
| Negative                          | 12      | 27.7   | 8.5   | 2.4  | 0.014*         |
| Positive                          | 11      | 18.5   | 7.8   | 2.3  |                |

SD - Standard deviation, SE - Standard error. *Statistically significant.

Figure 2: A 62-year-old male, a chronic smoker, presented with complaints of cough, chest pain, shortness of breath and weight loss. CECT in axial section (e) shows heterogeneously enhancing irregular mass with spiculated margins in the right middle lobe (black arrow). Colour-coded maps of CTP parameters (a) blood flow (BF), (b) blood volume (BV), (c) mean transit time (MTT), (d) permeability/flow extraction (FE) show predominant green, blue, and yellowish colors in the lesion, indicating low perfusion of the mass. (BF- 50.1 mL/100 g/min, BV- 3.9 mL/100 g, MTT- 5.3 s, FE- 18.8 mL/100 g/min.). Histopathology slides H and E-stained section (f), 10x, shows nests of tumor cells, carbon pigment near the right-hand side of the image. Immunohistochemistry (IHC) for p63 (g) showing intense nuclear positivity, 10x, proven as moderately differentiated squamous cell carcinoma (SCC)

P = 0.010) and in FE (f = 4.849, P = 0.013) [Table 5]. The Tukey post-hoc test revealed significant pairwise differences between T2 and T4 lesions in BF (mean average difference: 23.59 mL/100 g/min, P = 0.030), in BV (mean average difference: 2.42 mL/100 g, P = 0.007) and in FE (mean average difference: 11.65 mL/100 g/min, P = 0.011). Correlation of the perfusion parameters to metastatic status also showed statistically significant differences.
in the BF ($f = 4.712, P = 0.014$) and in BV ($f = 4.285, P = 0.020$) \[Table 6\]. Post-hoc Tukey test showed significant differences between non-metastatic (M0) and extrathoracic metastasis (M1b and M1c) lesions in BF (mean average difference: 18.13 mL/100 g/min, $P = 0.017$) and in BV (mean average difference: 1.44 mL/100 g, $P = 0.031$). Still, no statistically significant information was seen between TNM stage III and IV groups.

CTP parameters showed significant correlations among themselves. BF exhibited strong positive correlation with BV ($r = 0.877, P < 0.001$) and FE ($r = 0.707, P < 0.001$). BV exhibited a strong positive correlation with FE ($r = 0.855, P < 0.001$) as well. A strong positive correlation was seen between MTT and FE ($r = 0.515, P < 0.001$). In effect, FE showed strong positive correlations with all the other parameters.

**DISCUSSION**

The stage of presentation and the histological subtype decide the treatment plan for lung cancer. CTP parameters have been used for differentiating lung malignancy from benign nodules.\[14\] Pathological features such as microvessel density (MVD) and vascular endothelial growth factor (VEGF) expression have shown a good correlation with the same.\[15\] The emerging medical drugs for lung carcinoma are directed against tumour angiogenesis, thus halting cancer progression by suppressing the tumoral blood supply.\[16\] Among medical therapy, platinum-based chemotherapeutic drugs are used for SCC, whereas in non-squamous subtypes, targeted therapies are used depending on the lesion's mutational analysis. These drugs target vessel neogenesis (such as bevacizumab) or cells with endothelial growth factor receptor (EGFR) changes (such as erlotinib and gefitinib).\[9\] Tumours of lower perfusion show poor response to chemotherapy because of decreased drug delivery at the lesion site. Also, they are more hypoxic, thereby resulting in reduced radiosensitivity.\[17\]

Selection of eligible patients for these drugs and their response assessment requires the evaluation of tumour neovascularisation. Though Response Evaluation Criteria in Solid Tumours (RECIST) is the gold standard for response assessment, it is based on size criteria. Instead, CTP assesses the tumour perfusion, revealing the changes even before the size changes.\[18\] Also, low perfused tumours are likely to have poor drug delivery and tissue hypoxia, thereby leading to inadequate response to chemo-radiation.\[19\] CTP can identify poorly perfused tumours; this might help in customising the treatment regimen, and subtype identification can also help in treatment planning.

Literature review showed contradictory results of studies that have tried to characterise lung malignancy subtypes with CTP parameters \[Table 7\]. Bevilacqua *et al.*\[13\] and Shi *et al.*\[19\] showed statistically significant results on the CTP parameters among different subtypes. Mandeville *et al.*\[20\] found a significant difference in permeability between AC and SCC. Few other studies documented...
higher perfusion of AC than squamous histology without statistical significance,[9,21,22] whereas other studies showed no differences at all.[23,24]

Two cases of AC that showed very low perfusion and skewness of data were located in the periphery and were small in size. Peripherally located tumours probably receive predominant pulmonary circulation supply, which might not initiate angiogenesis yet at a smaller size.[13] Another possibility is the presence of significant necrosis in the lesion, thereby resulting in low perfusion.

Further analysis (N = 44) showed statistically significant differences among the subtype’s perfusion parameters. BF and BV were significantly higher in AC in comparison to SCC. A similar observation was documented by Bevilacqua et al.[13] with a higher mean BF in AC compared to SCC. Only BF between AC and SCC was assessed in their study, limiting them to comment on other perfusion parameters. We analysed the other three parameters as well (BV, MTT and FE) and included PDC, though PDC did not reveal any significant differences in perfusion to AC or SCC.

Our study also demonstrated significantly higher permeability in AC than SCC, which is in concordance with Shi et al.[19] Permeability was the main perfusion parameter in their study that showed statistically significant differences between three subtypes (AC, SCC

### Table 5: Analysis of CT perfusion parameters in different T stage groups (Results by ANOVA)

| Perfusion parameter | T stage | n   | Mean   | Std. Deviation | Std. Error | 95% Confidence Interval for Mean | F   | Sig (P) |
|---------------------|---------|-----|--------|----------------|------------|---------------------------------|------|---------|
| BF                  | T1      | 1   | 9.40   |                |            |                                 |      |         |
|                     | T2      | 5   | 38.84  | 14.62         | 6.54       | 20.69 - 56.99                   | 3.573| 0.037*  |
|                     | T3      | 4   | 63.40  | 19.15         | 9.58       | 32.93 - 93.87                   |      |         |
|                     | T4      | 36  | 62.43  | 19.06         | 3.18       | 55.98 - 68.88                   |      |         |
|                     | Total   | 46  | 58.80  | 20.91         | 3.08       | 52.59 - 65.01                   |      |         |
| BV                  | T1      | 1*  | 0.63   |                |            |                                 |      |         |
|                     | T2      | 5   | 2.46   | 0.85          | 0.38       | 1.40 - 3.52                     | 5.145| 0.010*  |
|                     | T3      | 4   | 4.53   | 0.79          | 0.39       | 3.27 - 5.78                     |      |         |
|                     | T4      | 36  | 4.88   | 1.69          | 0.28       | 4.31 - 5.45                     |      |         |
|                     | Total   | 46  | 5.13   | 1.90          | 0.27       | 4.96 - 5.30                     |      |         |
| MTT                 | T1      | 1*  | 4.01   |                |            |                                 |      |         |
|                     | T2      | 5   | 4.30   | 0.70          | 0.31       | 3.43 - 5.17                     | 3.055| 0.580   |
|                     | T3      | 4   | 4.95   | 0.73          | 0.37       | 3.78 - 6.12                     |      |         |
|                     | T4      | 36  | 5.30   | 0.89          | 0.15       | 5.00 - 5.60                     |      |         |
|                     | Total   | 46  | 5.13   | 0.91          | 0.13       | 4.86 - 5.40                     |      |         |
| FE                  | T1      | 1*  | 3.20   |                |            |                                 |      |         |
|                     | T2      | 5   | 12.14  | 5.34          | 2.39       | 5.51 - 18.77                    | 4.849| 0.013*  |
|                     | T3      | 4   | 19.55  | 3.45          | 1.73       | 14.06 - 25.04                   |      |         |
|                     | T4      | 36  | 23.79  | 8.54          | 1.42       | 20.90 - 26.68                   |      |         |
|                     | Total   | 46  | 21.70  | 9.04          | 1.33       | 19.02 - 24.39                   |      |         |

**BF** - Blood flow in mL/100 g/min, **BV** - Blood volume in mL/100 g, **MTT** - Mean transit time in s, **FE** - Flow extraction or permeability in mL/100 g/min. *Single lesion was present so omitted from ANOVA. *Statistically significant.

### Table 6: Analysis of CT perfusion parameters in non-metastatic and metastatic groups (Results by ANOVA)

| Perfusion parameter | M stage | n   | Mean   | Std. Deviation | Std. Error | 95% Confidence Interval for Mean | F   | Sig (P) |
|---------------------|---------|-----|--------|----------------|------------|---------------------------------|------|---------|
| BF                  | M0      | 20  | 65.99  | 18.70         | 4.18       | 57.24 - 74.74                   | 4.712| 0.014*  |
|                     | M1a     | 8   | 65.42  | 19.74         | 6.98       | 48.91 - 81.92                   |      |         |
|                     | M1b&c   | 18  | 47.87  | 19.94         | 4.70       | 37.95 - 57.78                   |      |         |
|                     | Total   | 46  | 58.80  | 20.91         | 3.08       | 52.59 - 65.01                   |      |         |
| BV                  | M0      | 20  | 5.03   | 1.97          | 0.44       | 4.11 - 5.95                     | 4.285| 0.020*  |
|                     | M1a     | 8   | 5.19   | 1.38          | 0.49       | 4.03 - 6.34                     |      |         |
|                     | M1b&c   | 18  | 3.59   | 1.43          | 0.34       | 2.88 - 4.30                     |      |         |
|                     | Total   | 46  | 4.49   | 1.80          | 0.27       | 3.96 - 5.03                     |      |         |
| MTT                 | M0      | 20  | 5.08   | 0.92          | 0.21       | 4.65 - 5.51                     | 0.741| 0.483   |
|                     | M1a     | 8   | 5.49   | 0.90          | 0.32       | 4.73 - 6.34                     |      |         |
|                     | M1b&c   | 18  | 5.03   | 0.92          | 0.22       | 4.58 - 5.49                     |      |         |
|                     | Total   | 46  | 5.13   | 0.91          | 0.13       | 4.86 - 5.40                     |      |         |
| FE                  | M0      | 20  | 23.15  | 8.99          | 2.01       | 18.94 - 27.36                   | 3.154| 0.053   |
|                     | M1a     | 8   | 26.45  | 7.98          | 2.82       | 19.78 - 33.12                   |      |         |
|                     | M1b&c   | 18  | 17.99  | 8.49          | 2.00       | 13.76 - 22.21                   |      |         |
|                     | Total   | 46  | 21.70  | 9.04          | 1.33       | 19.02 - 24.39                   |      |         |

**BF** - Blood flow in mL/100 g/min, **BV** - Blood volume in mL/100 g, **MTT** - Mean transit time in s, **FE** - Flow extraction or permeability in mL/100 g/min.
Table 7: Comparison of perfusion parameters in adenocarcinoma and squamous cell carcinoma in various studies

| Study               | BF in AC | BF in SCC | BV in AC | BV in SCC | MTT in AC | MTT in SCC | FE in AC | FE in SCC |
|---------------------|----------|-----------|----------|-----------|-----------|-----------|----------|-----------|
| Present study       | 69.9±21.0| 50.3±11.7 | 5.3±1.8  | 3.9±1.0   | 5.2±0.9   | 5.2±0.7   | 26.2±8.6 | 19.7±4.9  |
| Bevilacqua A et al. (2018) | 83.5±29.4| 57.0±27.2 | -        | -         | -         | -         | -        | -         |
| Shi J et al. (2013) | 74.7±28.2| 68.7±32.1 | 9.6±3.1  | 8.8±2.7   | 10.0±2.6  | 9.6±2.0   | 18.8±6.6 | 16.0±5.3  |
| Mandeville H C et al. (2012)* | -        | -         | 5.19     | 6.22      | -         | -         | -        | 17.3      |
| Bargavee V et al. (2016) | 64.1±19.7| 58.6±19.4 | 6.3±2.2  | 5.3±2.2   | 7.0±1.7   | 6.4±1.8   | 26.0±7.4 | 25.1±12.4 |
| Spira D et al. (2013)* | 37.0±3.4 | 32.9±3.7 | 6.5±0.6  | 6.0±0.9   | -         | -         | 30.9±5.1 | 26.3±3.2  |
| Sauter AW (2012)*    | 35.4±14.0| 35.5±13.0 | 7.3±6.3  | 10.0±7.6  | -         | -         | 27.8±10.3| 27.8±25.0 |

BF - Blood flow in mL/100 g/min, BV - Blood volume in mL/100 g, MTT - Mean transit time in s, FE - Flow extraction or permeability in mL/100 g/min. AC - adenocarcinoma, SCC - squamous cell carcinoma. *Used Patlak approach for perfusion map generation. Not evaluated in the study.

and SCLC, with \( P < 0.05 \); though high BF and BV have been seen in AC than SCC, statistical significance was not present. However, in their study, a statistically significant difference was seen in BF between AC and SCLC. We were limited in analysing SCLC separately as we had only a single case. Mandeville et al.\(^\text{[20]}\) also documented higher permeability in AC. Venkat et al.\(^\text{[9]}\) showed high BF, BV, MTT and permeability in AC compared to SCC without any statistically significant differences.

The histopathological differences between the subtypes might explain the differential perfusion parameters in them. AC has a higher neoangiogenesis with increased microvessel density (MVD) compared to SCC.\(^\text{[21]}\) CTP is a non-invasive imaging technique, yielding information reflecting the tumour’s angiogenic property at the microvessel level. This has a high value, especially in the targeted therapy era, as patients with lower perfusion, that is, lower angiogenic properties, might show inadequate response to the same.\(^\text{[9,17]}\)

Spira et al.\(^\text{[22]}\) and Sauter et al.\(^\text{[23]}\) showed contradictory results with the present study by using the Patlak perfusion evaluation technique, which showed low BF irrespective of the subtype compared to deconvolution technique studies, including our study. No previous comparison studies of different perfusion evaluation techniques in lung carcinoma have been mentioned in the literature, but studies on pancreatic tumours, renal tumours and colorectal cancer have shown significant differences in the perfusion parameters obtained using different calculation methods (deconvolution technique, Patlak approach and maximum-slope method). However, these results were not directly interchangeable among the various tumours.\(^\text{[16,20]}\)

We also obtained a cut-off value of perfusion parameters for diagnosing the AC from others by drawing the receiver operating characteristics (ROC) curve (N = 44) [Figure 5]. BF showed a better curve compared to other parameters with an optimum cut-off value of 58.85 mL/100 g/min, that is, if the BF was above the mentioned value, the lesion was likely to be AC with a sensitivity of 73.7% and a specificity of 72%. No previous studies in the literature have predicted the cut-off value of CTP parameters to characterise lung cancer subtypes. However, this needs to be evaluated in a larger cohort for diagnostic accuracy. The non-invasive method in subtype characterisation might help early treatment initiation, especially in AC, which benefits from antiangiogenic therapies.

Statistically significant lower perfusion (BF, BV and FE) was observed in P63-positive lesions compared to P63-negative lesions. BF, BV and FE were higher in TTF-1 positive tumours than in TTF-1 negative tumours but did not show statistical significance. These results are in concordance with the above observation as SCC is usually P63 positive and AC is usually TTF-1 positives. Determining the IHC status by a non-invasive method can help in treatment determination. Other IHC markers such as Napsin, CK-7, CK-20 and P40 were shown to have no statistically significant correlation with any of the perfusion parameters.

Significantly low BF, BV and permeability values were seen in T1 and T2 groups compared to T3 and T4 stages [Figure 6]. This information is important because T1, T2 lesions without nodal metastasis can undergo curative resection and may suggest possible perfusion differences among the operable and inoperable lung cancer cases, which needs to be further evaluated with an appropriate cohort. Zhou et al.\(^\text{[27]}\) concluded that low BF in T1b tumours can predict lymph node metastasis.
CONCLUSIONS

In the emerging era of targeted therapy for lung cancer, our study attempts to study the vascular dynamics of the tumours by using non-invasive CTP, thus helping in the differentiation of adenomatous from the non-adenomatous subtype of lung cancer. CTP can also detect adenocarcinoma with low perfusion parameters which will not be benefited from targeted chemotherapy. The CTP can also be useful during a biopsy in case of a large heterogeneous tumour and to assess the chemotherapy response.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Bradley SH, Abraham S, Callister ME, Grice A, Hamilton WT, Lopez RR, et al. Sensitivity of chest X-ray for detecting lung cancer in people presenting with symptoms: A systematic review. Br J Gen Pract 2019;69:e27-35.
3. Rami-Porta R, Call S, Dooms C, Obiols C, Sánchez M, Travis WD, et al. Lung cancer staging: A concise update. Eur Respir J 2018;51. doi: 10.1183/13993003.00190-2018.
4. Gharraf HS, Mehana SM, ElNagar MA. Role of CT in differentiation between subtypes of lung cancer; is it possible? Egypt J Bronchol 2020;14:1-7.
5. Kajiwara N, Akata S, Uchida O, Usuda J, Ohira T, Kawate N, et al. Cine MRI enables better therapeutic planning than CT in cases of possible lung cancer chest wall invasion. Lung Cancer 2010;69:203-8.
6. Bandi V, Lunn W, Ernst A, Eheberth R, Hoffmann H, Herth FJ. Ultrasound vs CT in detecting chest wall invasion by tumor: A prospective study. Chest 2008;133:881-6.
7. Miles KA, Hayball MP, Dixon AK. Functional images of hepatic perfusion obtained with dynamic CT. Radiology 1993;188:405-11.
8. Miles KA. Perfusion CT for the assessment of tumour vascularity: Which protocol? Br J Radiol 2003;76(Suppl 1):S36-42.
9. Venkat B, Sharma S. Whole tumour CT perfusion in non-small cell lung cancer: Evaluation of perfusion parameters prior to initiation of therapy. Int J Contemp Med Res 2015;3:8.
10. Miles KA. Perfusion imaging with computed tomography: Brain and beyond. Eur Radiol Supplements 2006;16:M37-43.
11. Sahani DV. Perfusion CT: An overview of technique and clinical applications. In Proceedings of the International Society for Magnetic Resonance in Medicine. Vol 18. 2010. p. 1-12.
12. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. CA Cancer J Clin 2017;67:93-9.
13. Bevilacqua A, Gavelli G, Baiocco S, Barone D. CT perfusion in patients with lung cancer: Squamous cell carcinoma and adenocarcinoma show a different blood flow. BioMed Res Int 2018;2018: doi: 10.1155/2018/6942131.
14. Huang C, Liang J, Lei X, Xu X, Xiao Z, Luo L. Diagnostic performance of perfusion computed tomography for differentiating lung cancer from benign lesions: A meta-analysis. Med Sci Monit 2019;25:3485-94.
15. Ma SH, Xu K, Xiao ZW, Wu M, Sun ZY, Wang ZX, et al. Peripheral lung cancer: Relationship between multi-slice spiral CT perfusion imaging and tumor angiogenesis and cyclin D1 expression. Clin Imaging 2007;31:165-77.
16. Toccoli N, Remy-jardin M, Copin MC, Scheperee EL, Mansier E, Jaillard S, et al. Assessment of non–small cell lung cancer perfusion: Pathologic-CT correlation in 15 patients. Radiology 2010;257:863-71.
17. Petralia G, Bonello L, Viotti S, Preda L, d’Andrea G, Bellomi M. CT perfusion in oncology: How to do it. Cancer Imaging 2010;10:8-19.
18. Miles KA. Functional computed tomography in oncology. Eur J Cancer 2002;38:2079-84.
19. Shi J, Schmid-Bindert G, Fink C, Sudaska S, Apfalter P, Pilz LR, et al. Dynamic volume perfusion CT in patients with lung cancer: Baseline perfusion characteristics of different histological subtypes. Eur J Radiol 2013;82:e894-900.
20. Mandeville HC, Ng QS, Daley FM, Barber PR, Pierce G, Finch J, et al. Operable non–small cell lung cancer: Correlation of volumetric helical dynamic contrast-enhanced CT parameters with immunohistochemical markers of tumor hypoxia. Radiology 2012;264:581-9.
21. Li Y, Yang ZG, Chen TW, Chen HJ, Sun YJ, Lu YR. Peripheral lung carcinoma: Correlation of angiogenesis and first-pass perfusion parameters of 64-detector row CT. Lung Cancer 2008;61:44-53.
22. Spira D, Neumeister H, Spira SM, Hetzel J, Spengler W, von Weyhren CH, et al. Assessment of tumor vascularity in lung cancer using volume
Arimbrakunnan, et al.: Computed tomography perfusion in primary lung cancer

perfusion CT (VPCT) with histopathologic comparison: A further step toward an individualized tumor characterization. J Comput Assist Tomogr 2013;37:15-21.

23. Sauter AW, Winterstein S, Spira D, Hetzel J, Schulze M, Mueller M, et al. Multifunctional profiling of non–small cell lung cancer using 18F-FDG PET/CT and volume perfusion CT. J Nucl Med 2012;53:521-9.

24. Nakano S, Gibo J, Fukushima Y, Kaira K, Sunaga N, Taketomi-Takahashi A, et al. Perfusion evaluation of lung cancer: Assessment using dual-input perfusion computed tomography. J Thorac Imaging 2013;28:253-62.

25. Deniffel D, Boutelier T, Labani A, Ohana M, Pfeiffer D, Roy C. Computed tomography perfusion measurements in renal lesions obtained by Bayesian estimation, advanced singular-value decomposition deconvolution, maximum slope, and Patlak models. Intermodel agreement and diagnostic accuracy of tumor classification. Invest Radiol 2018;53:477-85.

26. Goh V, Halligan S, Bartram CI. Quantitative tumor perfusion assessment with multidetector CT: Are measurements from two commercial software packages interchangeable? Radiology 2007;242:777-82.

27. Zhou H, Xiong Z, Liu JK, Chen SX, Zhou ML, Zhou JH, et al. Low tumor blood flow assessed with perfusion CT correlates with lymphatic involvement in patients with stage T1b non–small cell lung cancer. Thorac Cancer 2013;4:131-7.

28. Ovali GY, Sakar A, Göktan C, Çelik P, Yorgancıoğlu A, Nese N, et al. Thorax perfusion CT in non–small cell lung cancer. Comput Med Imaging Graph 2007;31:686-91.