Aims and objectives

Neoangiogenesis is the most critical and crucial aspect of cancer growth and its spread. Functional imaging techniques are complementing the existing morphological imaging techniques in this regard. Of the large number of functional imaging techniques available directed at assessing tumour metabolism and microcirculation, CT perfusion (CTP) allows non-invasive evaluation of the tumour vascularity\(^1\). In addition to being widely available and relatively cheaper, there is linear relationship between iodine concentration and tissue attenuation making the quantification simpler \(^2\). And with the commercially available vendor based softwares, CTP is the least cumbersome of all functional imaging techniques.

CTP is a dynamic study wherein tissue density changes are assessed following intravenous administration of iodinated contrast medium. The various perfusion parameters measured reflect the micro-vascular environment in the tissue. Blood flow (BF ml/100g/min) gives the flow rate through vasculature in tissue region. BF is a marker of tissue vascularity and tumour grade. Blood volume (BV ml/100g) gives the volume of flowing blood within a vasculature in tissue region and is a marker of tumour vascularity. Mean transit time (MTT seconds) is the time taken by the blood to travel from artery to vein and it reflects the perfusion pressure. Permeability surface area product (PS ml/100g/min) is the permeability or "leakiness" of the vessel and hence the maturity of the blood vessels \(^3\).

The purpose of this study is to determine the differences in perfusion parameters among various morphological attributes of non small cell lung carcinoma (NSCLC) - histological type, stage, size and location by CTP.
Methods and materials

The institutional ethics committee approved this study and informed consent was obtained from all patients prior to enrolment in the study. Patients were selected according to the following criteria - (1) histopathologically or cytologically proven cases of non-small cell carcinoma of lung (2) No prior chemotherapy/radiotherapy for the lung cancer (3) No contraindications to contrast medium administration.

85 patients (67 males and 18 females) were enrolled in the study. Male to female ratio was 3:1. Mean age of the patients was 57 years (34 to 80 years) with maximum number of patients in the seventh decade.

CT perfusion of chest was performed with a 64-slice MDCT scanner with Z-axis coverage of 14cm. The following protocol was used - First a non contrast CT (NCCT) of chest was acquired with following parameters: 100kV, 50-220 mA with automated tube current modulation, 0.8sec rotation time, 5mm thickness and total exposure time of 5 sec. The NCCT images were used to localise the tumour and to determine the scan position to cover the entire tumour volume.

CTP was performed after injection of 50ml of iodinated contrast medium at a rate of 5ml/sec with an automated pressure injector through the antecubital vein on the side opposite to the tumour to reduce streak artifacts from large veins, followed by injection of 30ml of normal saline at the same rate. 21 passes of helical CT in shuttle mode was performed after 5 seconds delay for a duration of 35.86 seconds. The following parameters were used: 100kV, 50-220 mA with automated tube current modulation, 0.4sec rotation time, 5mm thickness and noise index 15 and reconstructed at 0.625mm interval. Scan was performed in quiet calm breathing to reduce motion artifacts.

Then contrast enhanced CT (CECT) of the chest and upper abdomen was performed from thoracic inlet to the level of adrenal glands after 1.25ml/kg of iodinated contrast medium administration with the following parameters: 100kV, 50-220 mA with automated tube current modulation, 0.8sec rotation time, 0.625mm thickness and total exposure time of 5 sec.

CTP images were transferred to the commercially available vendor based program using deconvolution technique for the generation of CTP maps. Attenuation thresholds were fixed to include lungs and mediastinum and exclude bones. Arterial input was obtained using region of interest (ROI) (4-6 pixel size) placed over aorta or its branches depending on the location of tumour. Last pre-enhancement and post enhancement images were chosen. Then the program generated the functional colour maps. Unprocessed source
image and base image were displayed for drawing the ROI on the tumour. A freehand ROI was drawn in the tumour in the phase demonstrating maximal enhancement excluding necrotic areas (as depicted on unprocessed source images and base images), atelectatic lung, vessels and calcifications. Values of BV, BF, MTT & PS were measured in all sections depicting the tumour and the mean value was calculated.

**Statistical analysis:** Comparison of means of perfusion parameters among various histological subtypes, location, stage and size of tumours were done using student’s t tests. The mean difference, SD of the differences, and 95% limits of agreement (mean difference ± 2SD) were calculated for each of the four perfusion parameters. Two-tailed tests for 95% confidence were carried out for each category.
Results

PERFUSION PARAMETERS AMONG VARIOUS HISTOLOGICAL TYPES OF LUNG CANCER

Our study group consisted predominantly of patients with squamous cell carcinoma i.e. 55/85 (64.7%) followed by adenocarcinoma i.e. 21/85 (24.7%). Among males, squamous cell carcinoma was the most common histological type i.e. 48/67 (71.6%) followed by adenocarcinoma i.e. 14/67 (20.9%). Among females, squamous cell carcinoma and adenocarcinoma were equally seen i.e. 7/18 (38.9%) each.

No statistically significant difference was found in the perfusion parameters among various histological subtypes (p>0.05). However, BF and BV values were higher in adenocarcinoma than in squamous cell carcinoma as shown in table 1.

<table>
<thead>
<tr>
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<th>SCC(n=55)</th>
<th>ADENO (n=21)</th>
<th>ADENOSQ (n=3)</th>
<th>LARGE (n=6)</th>
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<tbody>
<tr>
<td>BF</td>
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<td>64.101</td>
<td>62.54</td>
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<tr>
<td>SE</td>
<td>2.638</td>
<td>4.269</td>
<td>11.295</td>
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<tr>
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<td>5.35</td>
<td>6.31</td>
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<tr>
<td>SE</td>
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<tr>
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<td>1.023</td>
<td>0.724</td>
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<tr>
<td>PS</td>
<td>25.078</td>
<td>26.040</td>
<td>19.933</td>
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<tr>
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<td>1.558</td>
<td>2.522</td>
<td>6.672</td>
<td>4.718</td>
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Table 1: Comparison of perfusion parameters among various histological subtypes.

Fig 1 shows CTP images in a case of squamous cell carcinoma

Fig 2 shows CTP images in a case of adenocarcinoma

PERFUSION PARAMETERS BETWEEN CENTRAL AND PERIPHERAL LUNG TUMOURS

Centrally located tumours were predominant in our study i.e. 54/85 (63.5%). Among the centrally located tumours, squamous cell carcinoma was the most common i.e. 42/54 (77.8%) followed by adenocarcinoma i.e. 10/54 (18.5%). Among peripherally located tumours, squamous cell carcinoma (13/31 - 41.9%) and adenocarcinoma (11/31 - 35.5%) had nearly equal distribution.

No statistically significant difference was found in the perfusion parameters between central and peripheral tumours (p>0.05). However, BF and BV values were higher in central tumours than in peripheral tumours as shown in table 2.
Table 2: Comparison of perfusion parameters between central and peripheral tumours

Table 3: Comparison of perfusion parameters among various stages.

PERFUSION PARAMETERS AMONG DIFFERENT STAGES OF LUNG CANCER

Our study had patients predominantly in stage IIIB (49/85-57.7%) followed by stage IV (30/85-35.3%), stage IIIA (5/85 - 5.9%) and stage IIA (1/85 - 1.1%).

No statistically significant difference in perfusion parameters were found in different stages (p>0.05). However, BF and BV values were higher in stage IIIB than in stage IV as shown in table 3.

PERFUSION PARAMETERS IN DIFFERENT TUMOUR SIZES (#5cm AND >5cm)

The study group was dichotomised into tumours #5cm and tumours >5cm. 32 patients had tumour size #5cm and 53 patients had tumour size >5cm.
Statistically significant difference was found in BF value (p<0.01) between tumours #5cm and tumours >5cm with higher values of BF in tumours #5cm. Rest of perfusion parameters were not statistically significant as shown in table 4.

<table>
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<th>#5cm (n=32)</th>
<th>&gt;5cm (n=53)</th>
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<tr>
<td>BF</td>
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<td>54</td>
</tr>
<tr>
<td>BV</td>
<td>5.88</td>
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<tr>
<td>MTT</td>
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<td>6.96</td>
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<tr>
<td>PS</td>
<td>29.19</td>
<td>22.64</td>
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Table 4: Comparison of perfusion parameters in tumours #5cm and tumours >5cm.

Fig 7 shows CTP images in a tumour >5cm

Fig 8 shows CTP images in a tumour <5cm
**Fig. 1:** 62 year old male patient with squamous cell carcinoma of right lung. Perfusion maps A-unprocessed source image, B - Base image, C - BF (62.129), D - BV (2.89), E - MTT (3.54) and F - PS (10.153).

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Fig. 2: 70 year old male patient with adenocarcinoma of right upper lobe. Perfusion maps A-unprocessed source image, B - Base image, C - MTT (7.40), D - BF (111.91), E - BV (11.9) and F - PS (37.012).

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Fig. 3: 62 year old male patient with a central tumour in the left lung. Perfusion maps A- unprocessed source image, B - Base image, C - BF (78.213), D - BV (8.71), E - MTT (7.72) and F - PS (40.112).

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Fig. 4: 65 year old male patient with a peripheral tumour in the right lower lobe. Perfusion maps A-unprocessed source image, B - Base image, C - BF (44.789), D - BV (4.68), E - MTT (8.30) and F - PS (16.22).

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Fig. 5: 55 year old male patient with tumour in the right lower lobe with stage IV. Patient had liver metastasis at presentation (images not shown). Perfusion maps A-unprocessed source image, B - Base image, C - BF (56.040), D - BV (5.75), E - MTT (6.87) and F - PS (27.80).

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Fig. 6: 66 year old male patient with tumour in the left upper lobe with stage IIIB. Perfusion maps A-unprocessed source image, B - Base image, C - BF (79.215), D - BV (8.24), E - MTT (7.21) and F - PS (27.532).

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Fig. 7: 55 year old male patient with tumour in left lower lobe measuring >5cm. Perfusion maps A-unprocessed source image, B - Base image, C - BF (49.124), D - BV (4.42), E - MTT (5.80) and F - PS (18.294).

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Fig. 8: 65 year old male patient with tumour in right lower lobe measuring #5cm. Perfusion maps A-unprocessed source image, B - Base image, C - BF (63.76), D - BV (4.85), E - MTT (5.14) and F - PS (48.818).

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Conclusion

There were many variables affecting perfusion parameter values in lung cancer which include the histological subtypes, location of tumour, size and stage of the tumour. Regarding the values of perfusion parameters in various morphological attributes of NSCLC, studies had been published in literature with conflicting results.

1. In our study, there was no statistically significant difference in perfusion parameters between squamous cell carcinoma and adenocarcinoma however BF and BV values were higher in adenocarcinoma. Similar results have been published by Shi J et al (4) and Li Y et al (5). However, Ovali GY et al (6) found statistically significant higher BF values in squamous cell carcinoma. Li Y et al (5) found higher microvessel density (MVD) and BF values in adenocarcinoma and hence supports the result obtained in our study. Despite these results, CTP cannot reliably differentiate these two common histological subtypes.

2. There was no statistically significant difference in perfusion parameters between central and peripheral tumours, however higher BF and BV values were obtained in central tumours in our study. Similar results were obtained by Ovali GY et al (6). However, higher perfusion values in peripheral tumours were obtained by Kiessling F et al (1).

3. There was no statistically significant difference in perfusion parameters between tumours in stage IIIIB and stage IV, however higher BF and BV values were obtained in stage IIIIB tumours in our study. Similar results were obtained by Li Yet al (5) and Ovali GY et al (6). Neoangiogenesis is not just sufficient to cause distant metastasis, it requires interaction at the molecular level by a number of other mechanisms involving adhesion molecules, invasion of vessels and lymphatics etc (5).

4. Finally, statistically significant higher BF values were obtained in tumours #5cm than tumours >5cm (p<0.01). Similar results were obtained by Kiessling F et al (1), Li Y et al (5) and Shi J et al (4). As the tumour increases in size, the central areas undergo necrosis due to inadequate blood supply which in turn increases the interstitial pressure and decreases the perfusion of the enhancing peripheral part of the tumour (1).

5. Perfusion parameters are dependent on tumour size with higher BF values in smaller tumours. Perfusion parameters cannot reliably differentiate histological subtypes, location and stage of tumour.
Personal information

Dr. Bargavee Venkat, MD Resident, Department of Radio-Diagnosis, Indira Gandhi Medical college, Shimla - 171001, Himachal Pradesh, India

Dr. Sanjiv Sharma, MD, Professor, Department of Radio-Diagnosis, Indira Gandhi Medical college, Shimla - 171001, Himachal Pradesh, India


