CT perfusion in lung cancers for predicting treatment response and prognosis

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Aims and objectives

The focus of imaging in oncology has shifted in recent times from morphological imaging to functional imaging, providing parameters to predict response, monitor therapy and assess long term outcome(1). Of the large number of functional imaging techniques available, CT Perfusion (CTP) is widely available, easy to perform, relatively cheaper and direct correlation of contrast enhancement and iodine concentration to tissue vascularity(2).

Role of CTP in non small cell lung cancer (NSCLC) was assessed:

1. To evaluate the perfusion parameters in cytologically or histopathologically proven NSCLC and thereby predict the response of the tumour before the commencement of treatment.
2. To determine changes in perfusion at the completion of treatment to assess the response.
3. To find out which one of the perfusion parameters correlated well with treatment outcome as per RECIST 1.1 (Response Evaluation Criteria in Solid Tumours).

Four perfusion parameters namely - Blood flow (BF) ml/100g/min, Blood volume (BV) ml/100g, Mean Transit Time (MTT) seconds and Permeability surface area product (PS) ml/100g/min were assessed qualitatively and quantitatively.
Methods and materials

Sixteen patients were enrolled in the study. All patients underwent CTP and contrast enhanced computed tomography (CECT) of the thorax before the commencement of treatment and again at the end of treatment.

Steps in the acquisition of CTP:

1. The scan was done in supine position with feet first.
2. He/she was cannulated with 18G cannula through the antecubital vein in the side opposite to the side of tumour location to reduce beam hardening artifacts.
3. No separate motion correction program was available. Hence, patients were instructed and demonstrated to breathe in a shallow and calm manner. The breathing instructions were rehearsed well before the procedure. CTP was then performed in quiet calm breathing to reduce motion related artifacts.
4. For initial localization of the lesion, a non-contrast CT scan (NCCT) of the chest was done.
5. After lesion localization on NCCT, a 14 cm scan range for CTP was selected to include largest lesion area.
6. CTP was acquired after 5 second delay of intravenous injection of 50 ml of iodinated low osmolar non-ionic contrast material injected at a rate of 5 ml/s followed by 30ml of normal saline at a rate of 5 ml/s using an automated pressure injector.
7. 21 passes of helical CT was acquired for a total duration of 35.86 seconds. Thereby, the total duration of scan was 40.86 seconds. The scanning was performed in a single phase.
8. After 5 minutes, CECT chest and upper abdomen from the thoracic inlet to the level of adrenal glands was acquired with 1.25ml/kg of iodinated low osmolar non ionic contrast medium injected at the rate of 2.5 ml/s

Table 1: The table summarizes the parameters used in the study for the acquisition of NCCT, CTP and CECT of chest in 64 slice MDCT scanner.

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>NCCT</th>
<th>CTP</th>
<th>CECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan type</td>
<td>Helical</td>
<td>Volume helical shuttle</td>
<td>Helical</td>
</tr>
<tr>
<td>Rotation time(sec)</td>
<td>0.8</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Rotation length</td>
<td>Full</td>
<td>Full</td>
<td>full</td>
</tr>
<tr>
<td></td>
<td>Off</td>
<td>On</td>
<td>Off</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td>Shuttle mode</td>
<td>Off</td>
<td>On</td>
<td>Off</td>
</tr>
<tr>
<td>Number of shuttle passes</td>
<td>---</td>
<td>21</td>
<td>---</td>
</tr>
<tr>
<td>Pitch</td>
<td>0.984:1</td>
<td>1.375:1</td>
<td>0.984:1</td>
</tr>
<tr>
<td>Speed (mm/rotation)</td>
<td>39.3</td>
<td>55</td>
<td>39.3</td>
</tr>
<tr>
<td>Helical thickness (mm)</td>
<td>5</td>
<td>0.625</td>
<td>0.625</td>
</tr>
<tr>
<td>Coverage speed (mm/sec)</td>
<td>49.2</td>
<td>137.50</td>
<td>49.2</td>
</tr>
<tr>
<td>mA with automated dose reduction measures</td>
<td>50-220</td>
<td>50-220</td>
<td>50-220</td>
</tr>
<tr>
<td>kV</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Noise index</td>
<td>--</td>
<td>15</td>
<td>--</td>
</tr>
<tr>
<td>Delay (sec)</td>
<td>--</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Exposure time (sec)</td>
<td>5</td>
<td>35.86</td>
<td>5</td>
</tr>
<tr>
<td>Volume of contrast</td>
<td>--</td>
<td>50ml</td>
<td>1.25ml/kg</td>
</tr>
<tr>
<td>Speed of contrast injection (ml/sec)</td>
<td>--</td>
<td>5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Steps in the generation of CTP maps:**

Data obtained on CTP was transferred to an image processing vendor's commercial workstation. Perfusion maps of the chest were generated by Deconvolution technique using vendor’s software. The program estimates
tissue perfusion as the maximum slope of the tumor time-density curve divided by the peak arterial enhancement.

The following steps were followed for generating perfusion maps and measuring the perfusion parameters:

1. The attenuation threshold was adjusted to include whole lung fields and mediastinum and exclude bones.
2. Arterial input was obtained using region of interest (ROI) (2 - 6 pixel) placed in the aorta or its branches depending on the location of the tumor.
3. The last pre-enhancement and post enhancement image was chosen to generate the maps. Unprocessed source image, base image and functional colour maps were generated.
4. Functional maps were displayed on colour scale in the following range - BF (0-400), BV (0-10), MTT (0-10) and PS (0-20).
5. To evaluate the perfusion parameters of lung masses, a freehand ROI was drawn in the tumour in the phase demonstrating maximal enhancement excluding necrotic areas (as depicted on unprocessed source image and base image), atelectatic lung, vessels and calcifications.
6. Values of BV, BF, MTT & PS were measured in all sections depicting the tumour and the mean value was calculated.

Tumour response after therapy was classified according to RECIST 1.1. Patients with complete response and partial response were classified as responders; the patients with stable disease and progressive disease as non-responders.

**Statistical Analysis:**

Baseline perfusion parameters were compared between the responders and non-responders by the use of Student's t tests. Perfusion parameters before and after therapy were compared by use of the paired samples Student's t test. Intraobserver and interobserver agreements were measured and tested using Bland Altman analysis.
Results

1. Sixteen patients (15 males and 1 female) were enrolled in the study with mean age was 61.18 years (45 to 74 years).
2. 10 patients had squamous cell carcinoma (SCC), 3 patients had adenocarcinoma (ADENO), 2 patients had adenosquamous cell carcinoma (ADENOSQ) and 1 patient had large cell carcinoma (LARGE).
3. Centrally located tumours were 10 and peripherally located tumours were 6.
4. 6 patients belonged to stage IV, 8 patients to stage IIIB and 2 patients to stage IIIA.
5. Of the 16 patients, 11 patients received 2 cycles of platinum based chemotherapy followed by radiotherapy (56 Gy in 28 fractions over a period of 6 weeks).
6. Remaining 5 patients received only 2 cycles of chemotherapy. Of these 5 patients, 3 patients died due to disease (2 due to distant metastasis and 1 due to pulmonary thromboembolism), 1 patient was lost to follow up and 1 patient died unrelated to disease (road traffic accident).

Perfusion parameters were compared at baseline and at end of the treatment. For the 11 patients who received sequential chemoradiotherapy, follow up was done after 2 cycles of chemotherapy and at the end of radiotherapy. For the remaining 5 patients, follow up was done at the end of 2 cycles of chemotherapy. Of the 16 patients, 10 patients were categorised as partial response, 4 patients had stable disease and 2 patients had progressive disease. Hence, in our study, there were 10 responders and 6 non-responders. Perfusion parameters were compared between these two groups at baseline and at the end of treatment.

Table 2 shows the comparison of baseline perfusion parameters between responders and non-responders. **Baseline BF and PS values were higher in responders** and showed statistically significant difference (p=0.047 and p=0.028 respectively). Though, BV values were higher in responders than non-responders but the difference was not statistically significant (p=0.521). MTT values also did not show statistically significant difference (p=0.227). Similar results were published in literature by Wang et al (3) and Fraioli et al (4).

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>RESPONDERS (n=10)</th>
<th>NON-RESPONDERS (n=6)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV</td>
<td>Mean 6.649, SE 0.738, RANGE 5.173-8.125</td>
<td>Mean 5.96, SE 0.737, RANGE 4.486-7.430</td>
<td>0.521</td>
</tr>
<tr>
<td>BF</td>
<td><strong>75.442</strong></td>
<td><strong>6.227</strong></td>
<td><strong>62.988-87.868</strong></td>
</tr>
<tr>
<td>MTT</td>
<td>Mean 6.058, SE 0.476, RANGE 5.106-7.017</td>
<td>Mean 5.834, SE 0.834, RANGE 5.647-8.988</td>
<td>0.227</td>
</tr>
</tbody>
</table>
Table 2: Comparison of baseline perfusion parameters between responders and non-responders.

Among the responders, mean target lesion size (according to RECIST 1.1) decreased by 41% (-34 to -47%), BF values decreased by 17% (+7 to -50%), BV decreased by 25% (+16 to -60%), MTT decreased by 10.4% (+24 to -35%) and PS decreased by 38.4% (+13 to -65%) as shown in table 3. All the perfusion parameters decreased at the end of treatment among the responders.

Table 3: RECIST 1.1 and CT perfusion parameters in responders (n=10) (complete and partial response) at baseline and follow-up.

Fig 1 & 2 show CTP images in a responder at baseline and after treatment

Among the non-responders (patients with stable disease and progressive disease), mean target lesion size (according to RECIST1.1) increased by 8% (-50 to 81%), BF decreased by 2.4% (-45 to +35%), BV decreased by 24% (-71 to +32%), MTT decreased by 22% (-49 to +13%) and PS increased by 9% (-84 to +106%) as shown in table 4. There was increase in the mean target lesion size and PS value at the end of treatment. There was no statistically significant difference in the decrease in BF value between responders and non-responders.

Table 4: RECIST 1.1 and CT perfusion parameters in non-responders (n=10) (stable disease and progressive disease) at baseline and follow-up.
Table 4: RECIST and CT perfusion parameters in non-responders (n=6) (stable and progressive disease) at baseline and follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BASELINE</th>
<th>POST-CHEMOTHERAPY</th>
<th>POST-RADIOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST (mm)</td>
<td>67.6</td>
<td>53.3</td>
<td>39.5</td>
</tr>
<tr>
<td>BF</td>
<td>80</td>
<td>103</td>
<td>119.9</td>
</tr>
<tr>
<td>BV</td>
<td>5.3</td>
<td>8.65</td>
<td>10.17</td>
</tr>
<tr>
<td>MTT</td>
<td>4.35</td>
<td>5.55</td>
<td>8</td>
</tr>
<tr>
<td>PS</td>
<td>25.7</td>
<td>25.1</td>
<td>27.2</td>
</tr>
</tbody>
</table>

Fig 3 & 4 show CTP images in a non-responder at baseline and after treatment.

PS values found at the end of treatment predicted the development of distant metastasis. Out of the 16 patients, 8 patients had increase in PS value at the end of treatment than at baseline, 6 of these 8 patients developed distant metastasis on follow up within 3 months. At baseline it was 22.186±2.849 ml/100g/min and it increased to 30.106±2.557 ml/100g/min. Of the remaining 8 patients who had decrease in PS value, 3 of them already had distant metastasis in liver at presentation. At baseline, PS was 32.721±4.41 ml/100g/min and it decreased to 10.906±3.177 ml/100g/min.

An increase in PS value may indicate increased leakage from neoplastic vessels, which may be a precursor to the tumour invasion and metastasis. Even an increase in PS value by 2% at follow up resulted in the development of distant metastasis in 95% of patients. A decrease in PS value by 24% on follow up showed no development of distant metastasis in 95% of patients in a 6 month follow up period.

Fig 5 & 6 show CTP images in a non-responder at baseline and after treatment. There was 33% increase in PS value at the end of treatment. Fig 7 shows liver metastasis on CECT done 3 months after treatment.

One of the patients in responders group (classified based on RECIST1.1) had the perfusion parameters mentioned in table 5:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BASELINE</th>
<th>POST-CHEMOTHERAPY</th>
<th>POST-RADIOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST (mm)</td>
<td>67.6</td>
<td>53.3</td>
<td>39.5</td>
</tr>
<tr>
<td>BF</td>
<td>80</td>
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<tr>
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<tr>
<td>MTT</td>
<td>4.35</td>
<td>5.55</td>
<td>8</td>
</tr>
<tr>
<td>PS</td>
<td>25.7</td>
<td>25.1</td>
<td>27.2</td>
</tr>
</tbody>
</table>

Table 5: Trend in the perfusion parameters in one of the patient at baseline, post chemotherapy and post radiotherapy.

By considering only RECIST1.1, it had been classified as partial response. But there was persistent increase in all perfusion values. The patient on 6 weeks follow up had an increase in target lesion size of 55.6 mm, now categorised under progressive disease according to RECIST 1.1. Thus, a persistent increase in perfusion values at the end of
treatment signifies increased likelihood of progressive disease. Hence, in this particular case, perfusion parameters predicted the outcome better than the RECIST 1.1 alone.

Fig 8 & 9 show CTP images in a responder (classified as per RECIST 1.1) at baseline and after treatment. There was persistent increase in perfusion parameters despite reduction in size at the end of treatment. This patient on follow up developed increase in mean target lesion size (as shown in fig 10) and reclassified as progressive disease.

Intraobserver and interobserver coefficients of variation for BF, BV, MTT, PS were 0.05%, 0.45%, 0.24%, 0.41% and 0.05%, 0.34%, 0.26%, 11.1% respectively.
Fig. 1: A case of 66 year old male patient with squamous cell carcinoma of right upper lobe of lung. Images of CTP prior to commencement of treatment. a - Unprocessed source image - ROI is drawn with a freehand technique, b - Base image, c - Mean Transit time map - 6.6 seconds, d - Blood flow map - 68.7 ml/100g/min, e - Blood volume map - 6.6 ml/100g, f - Permeability surface area product - 40.53 ml/100g/min

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Fig. 2: Same patient as in figure 1. Images of CTP after completion of treatment. a - Unprocessed source image - ROI is drawn with a freehand technique, b - Base image, c - Mean Transit time map - 4.56 seconds, d - Blood flow map - 21.8 ml/100g/min, e - Blood volume map - 1.58 ml/100g, f - Permeability surface area product - 5.95 ml/100g/min. There is reduction in all the perfusion parameters. According to RECIST 1.1, the patient was classified as PARTIAL RESPONSE.

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**Fig. 3:** 46 year old female with adenosquamous cell carcinoma of the right lower lobe of lung. Images of CTP prior to commencement of treatment. a - Unprocessed source image - ROI is drawn with a freehand technique, b - Base image, c - Mean Transit time map - 5.62 seconds, d - Blood flow map- 59.59 ml/100g/min, e - Blood volume map - 5.0 ml/100g, f - Permeability surface area product - 20.79 ml/100g/min.

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Fig. 4: Same patient as in Figure 3. Images of CTP after completion of treatment. a - Unprocessed source image - ROI is drawn with a freehand technique, b - Base image, c - Mean Transit time map - 7.29 seconds, d - Blood flow map- 51.85 ml/100g/min, e - Blood volume map - 5.94 ml/100g, f - Permeability surface area product - 24.97 ml/100g/min. There was minimal reduction in BF values, increase in MTT, BV and PS values. According to RECIST 1.1, the patient was classified as STABLE DISEASE.

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Fig. 5: A case of 74 year old male patient with adenocarcinoma of right lower lobe of lung. Images of CTP prior to commencement of treatment. a - Unprocessed source image - ROI is drawn with a freehand technique, b - Base image, c - Mean Transit time map - 6.04 seconds, d - Blood flow map- 57.51 ml/100g/min, e - Blood volume map - 4.71 ml/100g, f - Permeability surface area product - 22 ml/100g/min.

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Fig. 6: Same patient as in figure 5. Images of CTP after completion of treatment. a - Unprocessed source image - ROI is drawn with a freehand technique, b - Base image, c - Mean Transit time map - 7.06 seconds, d - Blood flow map - 63.56 ml/100g/min, e - Blood volume map - 6.46 ml/100g, f - Permeability surface area product - 32.86 ml/100g/min. There was increase in all the perfusion parameters particularly PS value (33% increase). According to RECIST 1.1, the patient was classified as STABLE DISEASE.

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Fig. 7: Same patient as in fig 5 & 6 - CECT of abdomen done after 3 months showed liver metastasis

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Fig. 8: A case of 68 year old male patient with squamous cell carcinoma of left upper lobe of lung. Images of CTP prior to commencement of treatment. a - Unprocessed source image - ROI is drawn with a freehand technique, b - Base image, c - Mean Transit time map - 4.35 seconds, d - Blood flow map- 80 ml/100g/min, e - Blood volume map - 5.3 ml/100g, f - Permeability surface area product - 25.7 ml/100g/min.

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Fig. 9: Same patient as in fig 8. Images of CTP after completion of treatment. a - Unprocessed source image - ROI is drawn with a freehand technique, b - Base image, c- Mean Transit time map - 8 seconds, d - Blood flow map- 119.9 ml/100g/min, e - Blood volume map - 10.17 ml/100g, f- Permeability surface area product - 27.2 ml/100g/min. There was increase in all the perfusion parameters. According to RECIST 1.1, considering only the size of the lesion, the patient was classified as PARTIAL RESPONSE.

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Fig. 10: Same patient as in fig 8 & 9 - CECT of thorax - Axial section on follow up after 6 weeks showed increase in target lesion size and hence now reclassified as PROGRESSIVE DISEASE.

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Conclusion

Perfusion parameters reflect the neoangiogenesis in tumours. Direct correlation has been found between tumour perfusion parameters and biomarkers of angiogenesis such as microvessel density (MVD) and vascular endothelial growth factor (VEGF) in several tumours (5). RECIST 1.1 evaluates the treatment response only based on the size which is not sufficient. Functional imaging techniques such as CTP can assess the perfusion of the tumours and hence reveal early changes to treatment even before significant reduction in size may happen (6). Low tumour perfusion indicates less blood flow to the tumour which in turn impairs the delivery of the chemotherapeutic agents. Also hypoxia decreases radiosensitivity (5). Significance of various perfusion parameters in our study is as follows:

1. Higher baseline BF value before the commencement of treatment predicted good response.
2. Following treatment, no statistically significant difference was found in perfusion parameters in responders as well as non-responders however, there was greater decrease in BF value in responders than non-responders.
3. Increase in PS value at the end of treatment signified likelihood of development of metastasis.
4. Of the four perfusion parameters, BF and PS values correlated well with treatment outcome.
5. Persistent increase in BF and BV values in one patient proved to be a better predictor of response as compared to RECIST 1.1. But the limitation is number of patients. Therefore, it needs further evaluation in a larger series and at multiple centres.
6. Greater Z-axis coverage and whole tumour technique had resulted in good interobserver and intraobserver agreements and hence good reproducibility.
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References


