SciMedCentral

JSM Clinical and Medical Imaging: Cases and Reviews

Research Article

Whole Tumour CT Perfusion in Non-Small Cell Lung Cancer: Evaluation of Perfusion Parameters Prior to Initiation of Therapy

Bargavee Venkat[1]*, Sanjiv Sharma[1], Neeti Aggarwal[1], Sankaran M[2], Dinesh Sharma[1], and Malay Sarkar[3]

[1]*Department of Radio-Diagnosis, Indira Gandhi Medical College, India*
[2]*Management Studies, Bharathidasan Institute of Management, India*
[3]*Department of Pulmonary Medicine, Indira Gandhi Medical College, India*

***Corresponding author**
BargaveeVenkat, Department of Radio-Diagnosis, Indira Gandhi Medical College, Shimla, India – 171001; Tel: +91 9496805988; Email: bargavee@gmail.com

Submitted: 27 May 2017

Accepted: 18 January 2018

Published: 20 January 2018

Keywords
- Perfusion
- Computed tomography
- Thorax
- Blood flow
- Blood volume

Abstract

Objectives: To analyse and correlate the perfusion parameters measured by CT perfusion with different histological sub-types, stage and location of tumour and tumour volume in cases of Non-small cell lung cancer prior to initiation of therapy.

Materials and Methods: 85 patients with proven Non-small cell lung cancer underwent CT perfusion in a 64 slice multi-detector CT scanner. Whole tumour perfusion parameters - 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 measured. Each perfusion parameter was analysed and correlated with each other and with different histological sub-types, stage, location and volume of the tumour.

Results: There was statistically significant difference in BF, MTT and PS values in >50 cm3 and ≤50 cm3tumour volume groups (p= 0.001, 0.021 and 0.019 respectively). There was no statistically significant difference in perfusion parameters among different histological sub-types, stage and location of tumour, however, BV, BF and MTT values were higher in adenocarcinoma than in squamous cell carcinoma and higher in stage IV than in stage IIIB, BV and BF values were higher in central tumours than in peripheral tumours and MTT values were higher in peripheral tumours than in central tumours. There was strong positive correlation between BF and BV (r=0.7873, p<0.0001), BF and PS (r=0.6719, p<0.0001) and BV and PS (r=0.5793, p<0.0001). There was weak correlation between BF and tumour volume (r=0.3589, p=0.0298), MTT and BV (r=0.4275, p=0.0019) and location of tumour and histological sub-type of tumour (r=0.3838, p=0.0118).

Conclusion: CT perfusion done prior to initiation of therapy revealed significant correlation within perfusion parameters and also with tumour volume. Perfusion parameters may be related to tumour volume. No significant difference in perfusion parameters were found among different histological sub-types, stage and location of tumour.

ABBREVIATIONS

BF: Blood Flow; BV: Blood Volume; CECT: Contrast Enhanced Computed Tomography; CT: Computed Tomography; CTP : Computed Tomographic Perfusion; MTT: Mean Transit Time; MVD :Microvessel Density; NCCT : Non Contrast Enhanced Computed Tomography; NSCLC: Non Small Cell Lung Cancer; PS :Permeability Surface Product Ratio; RECIST : Response Evaluation Criteria In Solid Tumours; ROI : Region of Interest

INTRODUCTION

Lung cancer is the most common cause of cancer death worldwide. The World Health Organisation International Agency for Research on Cancer reported the global incidence of lung cancer at approximately 1.8 million new cases on 2012. The overall ratio of mortality to incidence is high with an estimated 1.59 million deaths per year around the world [1]. Treatment options available include surgery, radiotherapy, conventional chemotherapy and newer targeted therapies like erlotinib and bevacizumab. Various characteristics of non-small cell lung cancer such as histological sub-type, stage, volume and location of the tumour have a bearing on the choice of therapy.

Functional imaging techniques assessing tumour metabolism and vascularity are gaining popularity and are being increasingly used for treatment planning and for assessment of treatment response and prognosis. Neoangiogenesis, being the most critical and crucial aspect of cancer growth and its spread is assessed by CT perfusion which gives a direct in vivo assessment of tumour vascularity. It complements the existing morphological imaging techniques in assessing the tumour microenvironment which are often the target in cancer therapeutics. In addition

to being widely available and relatively cheaper, there is linear relationship between iodine concentration and tissue attenuation making the quantification simpler [2]. First report of measurement of perfusion parameters in body using spiral CT was published in 1993 by Miles et al. They described a dynamic computed tomographic technique for separate quantification of arterial and portal components of hepatic perfusion [3]. Leon Axel conceived the idea of CT perfusion as early as in 1979, just eight years after introduction of CT by Godfrey Hounsfield. But, earlier CTP suffered from poor reproducibility and limited Z-axis coverage. Better reproducibility of perfusion parameters is achieved with increasing Z-axis coverage in newer scanners and volumetric helical or shuttle modes covering the whole tumour. Computerized motion correction further helped in improved reproducibility [4]. Various studies were conducted to identify optimal time of acquisition. While rest of the perfusion parameters [BF, BV and MTT] requires a first pass scan for a shorter duration of 40-50 seconds, measurement of PS requires an extended second phase scan done typically 2-10 minutes after the first pass study [5]. The commercially available vendor based softwares have made CTP the least cumbersome of all functional imaging techniques.

Perfusion parameters measured by CTP correlated well with micovessel density [6,7], cyclin D1[6] and vascular endothelial growth factor expression [7]. With the emergence of targeted therapies in the treatment of non-small cell lung cancer, imaging techniques that assess tumour micro-environment such as CTP, have gained popularity for response assessment alongside the gold standard Response Evaluation Criteria in Solid Tumours (RECIST). RECIST1.1 assesses response of solid tumours to chemo-radiation based on change in size. Since CTP can assess the tumour perfusion, it can reveal early changes in treatment even before significant reduction in size may happen [8].

Tumours with low perfusion suffer from poor response to chemo-radiation due to tissue hypoxia. In this era of personalised cancer treatment, CTP performed prior to the commencement of treatment, could potentially identify tumours sensitive to chemo-radiotherapy and avoid expensive and ineffective treatment with potential side effects.

The purpose of the study is to analyse and correlate the perfusion parameters measured by CT perfusion prior to initiation of therapy with various characteristics of non-small cell lung cancer which have relevancein the choice of treatment.

MATERIALS AND METHODS

Patient selection

The institutional ethics committee approved this study and informed consent was obtained from all patients prior to enrolment in the study after explaining to them the complete procedure. Eighty five histologically proven cases of non-small cell lung cancer were included in this prospective study. Only patients with unresectable tumours or inoperable due to other reasons such as refusal to surgery or presence of co-morbidities were included. Patients who had undergone previous surgery or chemo-radiotherapy for lung cancer and patients with contraindications to contrast medium administration were excluded from this study.

Imaging protocol

CT perfusion 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 denotes the maturity of the blood vessels.

The CT perfusion of chest was performed with a 64-slice MDCT scanner (Light speed VCT Xte; GE Healthcare). Non contrast CT (NCCT) of chest was acquired to localise the tumour and to determine the scan range of 14cm in the Z-axis for CT perfusion (CTP) examination to cover the entire tumour volume. The following protocol was used - 100kV, 50-220 mA with automated tube current modulation, 0.8sec rotation time, 5mm thickness and total exposure time of 5 sec.

Then CTP was performed after injection of 50ml of iodinated contrast medium at a rate of 5ml/sec with an automated pressure injector (Stellant, MEDRAD) through the antecubital vein on the side opposite to the tumour to reduce streak artefacts from large veins followed by injection of 30ml of normal saline at the same rate. 21 scans in helical shuttle mode were acquired 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 artefacts.

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 (100kV, 50-220 mA with automated tube current modulation, 0.8sec rotation time, 0.625mm thickness and total exposure time of 5 sec).

Image processing

Series data containing the reformatted images covering the whole tumour were transferred to an image processing workstation – Advantage windows 4.2, GE Healthcare. Perfusion maps of the chest are generated by using software Perfusion CT 4 (GE) and perfusion deconvolution technique. The program estimates tissue perfsion as the maximum slope of the tumour time-density curve divided by the peak arterial enhancement. Attenuation thresholds were fixed to include lungs and mediastinum and exclude bones and calcifications. 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 (Figure 1). Last pre-enhancement and post enhancement images were chosen from the set of images. Then the program generated functional colour coded perfusion maps of BF, BV, MTT and PS (Figure 2). Unprocessed source image and base image were displayed for drawing the region of interest (ROI) on the tumour

(Figure 3). A freehand ROI was drawn in the tumour in the phase demonstrating maximum enhancement excluding necrotic areas, atelectatic lung, vessels and calcifications. Vessels were identified by virtue of their contrast opacification (Figure 3) and using maximum intensity projection. Necrotic areas were identified best on unprocessed source image by lack of enhancement. Values of BV, BF, MTT & PS were measured in all contiguous transverse sections depicting the tumour and the mean perfusion value was calculated for the whole tumour.

Estimation of tumour volume

The tumour is considered as a spheroid and volume was calculated by the product of π/6 and longest transverse, antero-posterior and cranio-caudal dimensions measured from multiplanar reconstructed images. The volumes of the tumours were then dichotomised into > 50 cm^3 and ≤ 50 cm^3groups.

Location of tumour

Central tumours were defined as tumours located within 2 cm of the proximal bronchial tree, heart, great vessels, trachea, or other mediastinal structures. Rests were classified as peripheral tumours.

Staging

TNM staging and stage grouping were done according to American Joint Committee on Cancer (AJCC) 7th edition [9].

Histological subtypes

Histology was done according to the current standards and classified based on WHO histological classification of the tumours of lung.

Statistical analysis

Analysis of variance (ANOVA) was performed on each of the perfusion parameters (BV, BF, MTT and PS) measured by CTP and different histological sub-types, tumour location (central vs peripheral), tumour volume (> 50 cm^3 and ≤ 50 cm^3) and stage groups. The measured perfusion parameters were treated as continuous and mean, standard deviation, standard error and lower and upper limits of 95% confidence interval were calculated on the data. F – value was calculated for each comparison. P-value ≤ 0.05 was treated as statistically significant difference. Spearman rank correlation, a non-parametric test was used to measure the degree of association between two variables. To control the family wise error rate [FWER], adjusted p-values were measured using Holm-Bonferroni method, which is a method to counteract the problem of multiple comparisons.

RESULTS AND DISCUSSION

All CT perfusion examinations were conducted without major complications. The images were of good quality and not degraded by artefacts. Motion artefacts were reduced drastically by good preparation and rehearsal of the patients prior to the study for calm and quiet breathing. Beam hardening artefacts from dense contrast material in major veins in thorax were reduced considerably by saline flush after injection of contrast material.

Characteristics of study participants

Eighty five patients (67 of them were male, 78.8%) were included in this study with a mean age of 61±2 years. As summarised in Table (1), 55 patients had squamous cell carcinoma (64.7%) constituting the major histological subtype followed by adenocarcinoma in 21 patients (24.7%). Centrally located tumours were seen in 54 patients (63.5%) and the rest of the tumours were peripherally located. Most of the tumours were >50 cm^3 in volume (62 patients, 72.9%). Majority (49 patients, 57.6%) patients were in stage IV followed by stage IIIB (30 patients, 35.3%). Table (2) summarises the mean, standard deviation and standard error of the perfusion parameters measured in the total cohort.

Variation of blood volume (BV) among various groups

There was no statistically significant difference in BV values among different histological subtypes, stage, location and volume of the tumours as shown in Table (3). However, BV values were higher in adenocarcinoma (6.3, 5.3-7.3) than in squamous cell carcinoma (5.3, 4.8-5.9), higher in central tumours (5.7, 5.1-6.3) than in peripheral tumours (5.4,4.5-6.2), higher in ≤50 cm^3 (6.1,

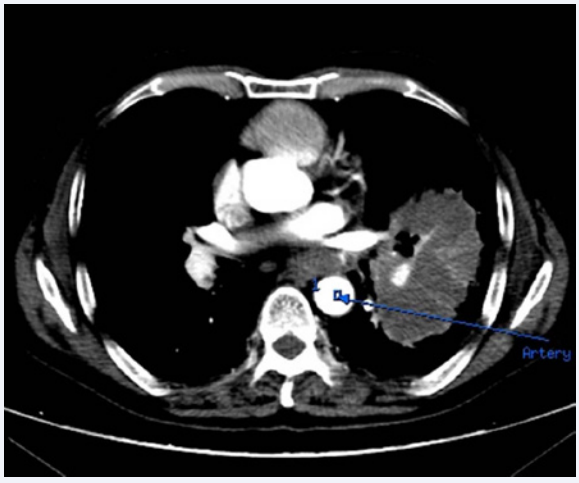

Figure 1 Arterial input was placed using region of interest in the descending thoracic aorta adjacent to the tumour.

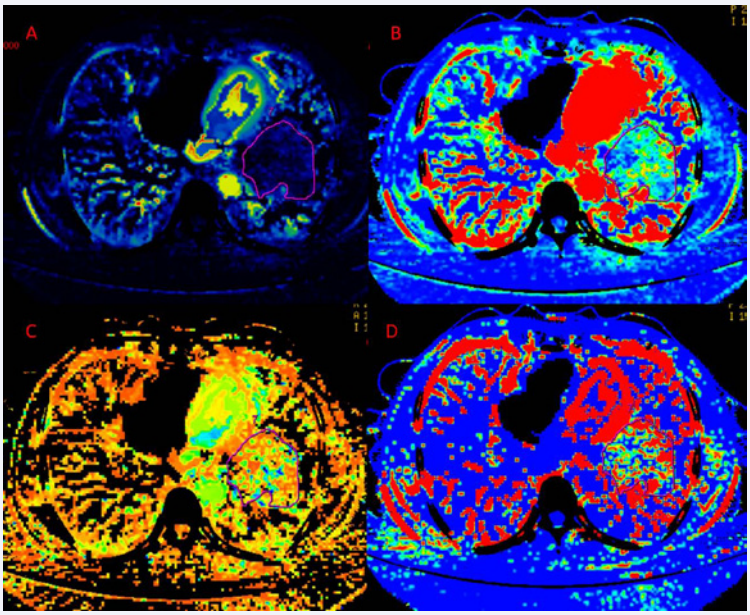

Figure 2 Functional colour coded maps of blood flow [A], blood volume [B], mean transit time [C] and permeability surface area product [D] were generated.

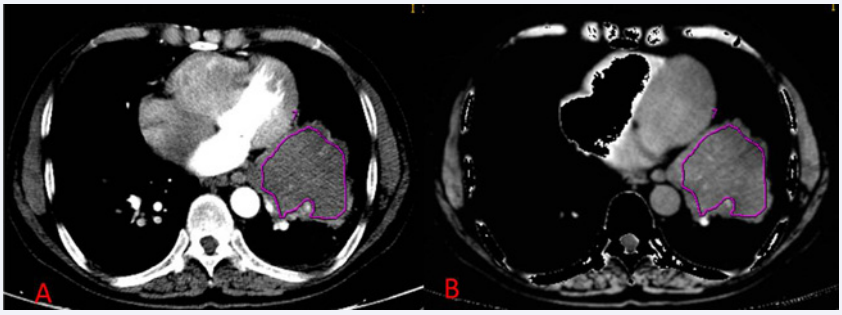

Figure 3 Unprocessed source image [A] and base image [B] were used to draw the region of interest [ROI]. Blood vessels were identified by virtue of their contrast opacification and were thus excluded from the ROI.

5.2-7.0) tumour volume group than in > 50 cm^3 group (5.4, 4.8-5.9), higher in stage IIIB (6.2, 5.1-7.3) than in stage IV (5.3, 4.8-5.8).

Variation of blood flow (BF) among various groups

Blood flow of tumours with ≤ 50 cm^3 volume (71.0, 62.5-79.5) was significantly higher than in tumours with >50 cm^3 volume (55.0, 50.4-59.5)(p = 0.001) as depicted in Table (4). No significant difference was found among histological subtypes, stage and location of tumours. However, BF values were higher in adenocarcinoma (64.1, 55.1-73.1) than in squamous cell carcinoma (58.6, 53.4-63.9), higher in central tumours (61.3, 55.9-66.7) than in peripheral tumours (55.9, 48.8-62.9), and higher in stage IIIB (63.6, 55.0-72.3) than in stage IV (57.7, 52.6-62.7).

Variation of mean transit time (MTT) among various groups

Mean transit time was significantly lower in tumours with ≤ 50 cm^3 volume (5.9, 5.2-6.6) than in tumours with >50 cm^3

Table 1: General characteristics of patients.

		Number (%)
1.	Gender	
	Male	67 (78.8)
	Female	18 (21.2)
2.	Type	
	Squamous cell carcinoma	55 (64.7)
	Adenocarcinoma	21 (24.7)
	Large cell carcinoma	6 (7.1)
	Adenosquamous carcinoma	3 (3.5)
3.	Location	
	Central tumour	54 (63.5)
	Peripheral tumour	31 (36.5)
4.	Volume	
	>50 cm^3	62 (72.9)
	≤50 cm^3	23 (27.1)
5.	Stage	
	Stage IV	49 (57.6)
	Stage IIIB	30 (35.3)
	Stage IIIA	5 (5.9)
	Stage IIB	1 (1.2)

Table 2: Summary of the perfusion parameters and age measured in all patients.

	MEAN	SD*	SE#	IQRα	CVβ	SKEWNESS	KURTOSIS	0%	25%	50%	75%	100%
AGE	60.858824	8.8279223	0.95752262	11.00	0.1450558	-0.6041272	0.21529048	34.00	55.00	66.00	80.00	85
BF[1]	59.310118	19.6431153	2.13059499	24.24	0.3311933	0.3556419	0.40703896	16.41	47.86	57.90	72.10	123.20
BV[2]	5.563294	2.2410278	0.24307360	2.60	0.4028239	0.9341145	1.67017637	1.30	4.20	5.10	6.80	13.77
MTT[3]	6.585176	1.7723307	0.19223626	1.90	0.2691394	0.8615696	0.85248767	2.80	5.50	6.13	7.40	12.27
PS[4]	25.112588	11.4002454	1.23653023	14.49	0.4539654	0.8081155	1.00280200	5.20	16.48	23.75	30.97	64.23

*- Standard deviation
#- Standard error
α- Interquartile range
β- Coefficient of variation
[1] – Blood Flow
[2] – Blood Volume
[3] – Mean Transit time
[4] – Permeability Surface area product

Table 3: ANOVA of blood volume (BV) among different types, locations, volume and stage of the tumour.

	N	Mean	SD*	SE#	95% Confidence Interval for Mean		Minimum	Maximum	F_Value	P_Value
					Lower Bound	Upper Bound				
Type										
SCC[1]	55	5.3	2.2	0.3	4.8	5.9	1.7	13.8		
Adeno Ca[2]	21	6.3	2.2	0.5	5.3	7.3	1.6	11.4		
Adenosq Ca[3]	3	5.3	0.8	0.4	3.4	7.2	4.4	5.9	1.066	0.368
Large cell Ca	6	5.0	3.2	1.3	1.6	8.4	1.3	10.5		
Total	85	5.6	2.2	0.2	5.1	6.0	1.3	13.8		
Location										
Central	54	5.7	2.2	0.3	5.1	6.3	1.7	13.8		
Peripheral	31	5.4	2.3	0.4	4.5	6.2	1.3	11.1	0.357	0.552
Total	85	5.6	2.2	0.2	5.1	6.0	1.3	13.8		
Volume										
>50 cm^3	62	5.4	2.3	0.3	4.8	5.9	1.3	13.8		
≤ 50 cm^3	23	6.1	2.1	0.4	5.2	7.0	2.7	11.4	2.019	0.159
Total	85	5.6	2.2	0.2	5.1	6.1	1.3	13.8		
Stage										
IV	49	5.3	1.7	0.2	4.8	5.8	1.3	10.5		
IIIB	30	6.2	2.9	0.5	5.1	7.3	1.6	13.8		
IIIA	5	4.6	1.2	0.5	3.1	6.1	3.6	6.6	1.830	0.148
IIB	1	3.3	.	.	.	.	3.3	3.3		
Total	85	5.6	2.2	0.2	5.1	6.0	1.3	13.8		

*- Standard deviation
#- Standard error
[1] – Squamous cell carcinoma
[2] - Adenocarcinoma
[3]- Adenosquamous carcinoma

volume (6.9, 6.4-7.3)(p=0.021) as depicted in Table 5. There was no significant difference in MTT values among other groups, though, values were higher in adenocarcinoma (7.0, 6.2-7.8) than in squamous cell carcinoma (6.4, 5.9-6.9), higher in peripheral tumours (6.8, 6.1-7.5) than in central tumours (6.5, 6.0-6.9) and higher in stage IIIB (6.9, 6.1-7.6) than in stage IV (6.5, 6.0-7.0).

Variation of permeability surface area product (PS) among various groups

Permeability surface area product was significantly higher in tumours with <50 cm^3 volume (29.8, 24.3-35.4) than in tumours with >50 cm^3 volume (23.4, 20.7-26.0) (p=0.019) as shown in Table (6). There was no significant difference in PS value among histological subtypes, stage and location of tumour.

Degree of association or correlation among variables (Tables 7-9)

Significant correlation was found among the perfusion parameters. There was strong positive correlation of BF with BV (r=0.7873, p<0.0001) and with PS (r=0.6719, p<0.0001). No correlation was found between BF and MTT (r=-0.0871, p=1.0000). There was strong correlation of BV with BF (as described above), with PS (r=0.5793, p<0.0001) and weak positive correlation with MTT (0.4275, p=0.0019). PS and MTT did not correlate (r=0.0248, p=1.0000).

There was weak correlation between BF and tumour volume (r=0.3589, p=0.0298). Rest of the perfusion parameters did not correlate with tumour volume. Also there was no significant

Table 4: ANOVA of blood flow (BF) among different types, locations, volume and stage of the tumour.

	N	Mean	SD*	SE#	95% Confidence Interval for Mean		Minimum	Maximum	F_Value	P_Value
					Lower Bound	Upper Bound				
Type										
SCC[1]	55	58.6	19.4	2.6	53.4	63.9	22.3	105.3		
Adeno Ca[2]	21	64.1	19.7	4.3	55.1	73.1	30.1	123.2	1.228	0.305
Adenosq Ca[3]	3	62.5	10.4	6.0	36.8	88.3	51.5	72.1		
Large cell Ca	6	47.3	23.2	9.5	22.9	71.6	16.4	79.2		
Total	85	59.3	19.6	2.1	55.1	63.5	16.4	123.2		
Location										
Central	54	61.3	19.8	2.7	55.9	66.7	22.3	123.2		
Peripheral	31	55.9	19.3	3.5	48.8	62.9	16.4	105.3	1.508	0.223
Total	85	59.3	19.6	2.1	55.1	63.5	16.4	123.2		
Volume										
>50 cm^3	62	55.0	18.0	2.3	50.4	59.5	16.4	90.7		
≤ 50 cm^3	23	71.0	19.6	4.1	62.5	79.5	31.5	123.2	12.718	0.001
Total	85	59.3	19.6	2.1	55.1	63.5	16.4	123.2		
Stage										
IV	49	57.7	17.6	2.5	52.6	62.7	16.4	92.5		
IIIB	30	63.6	23.1	4.2	55.0	72.3	22.3	123.2		
IIIA	5	51.8	15.2	6.8	33.0	70.7	30.1	68.7	0.954	0.419
IIB	1	47.7	.	.	.	.	47.7	47.7		
Total	85	59.3	19.6	2.1	55.1	63.5	16.4	123.2		

*- Standard deviation
#- Standard error
[1]Squamous cell carcinoma
[2]Adenocarcinoma
[3]Adenosquamous carcinoma

Table 5: ANOVA of mean transit time (MTT) among different types, locations, volume and stage of the tumour.

	N	Mean	SD*	SE#	95% Confidence Interval for Mean		Minimum	Maximum	F_Value	P_Value
					Lower Bound	Upper Bound				
Type										
SCC[1]	55	6.4	1.8	0.2	5.9	6.9	2.8	12.3		
Adeno Ca[2]	21	7.0	1.7	0.4	6.2	7.8	4.7	10.7		
Adenosq Ca[3]	3	6.1	1.0	0.6	3.7	8.6	5.5	7.3	0.999	0.398
Large cell Ca	6	7.2	2.2	0.9	4.9	9.6	5.2	10.3		
Total	85	6.6	1.8	0.2	6.2	7.0	2.8	12.3		
Location										
Central	54	6.5	1.7	0.2	6.0	6.9	2.8	12.3		
Peripheral	31	6.8	1.9	0.3	6.1	7.5	3.7	10.7	0.543	0.463
Total	85	6.6	1.8	0.2	6.2	7.0	2.8	12.3		
Volume										
>50 cm^3	62	6.9	1.8	0.2	6.4	7.3	3.7	12.3		
≤ 50 cm^3	23	5.9	1.6	0.3	5.2	6.6	2.8	10.3	5.502	0.021
Total	85	6.6	1.8	0.2	6.2	7.0	2.8	12.3		
Stage										
IV	49	6.5	1.6	0.2	6.0	7.0	3.7	12.3		
IIIB	30	6.9	2.1	0.4	6.1	7.6	2.8	10.7		
IIIA	5	6.1	1.5	0.7	4.3	8.0	5.1	8.5	0.948	0.422
IIB	1	4.3	.	.	.	.	4.3	4.3		
Total	85	6.6	1.8	0.2	6.2	7.0	2.8	12.3		

*- Standard deviation
#- Standard error
[1]Squamous cell carcinoma
[2]Adenocarcinoma
[3]Adenosquamous carcinoma

correlation of perfusion parameters with other variables (histological subtypes, stage and location of tumour) (p>0.05).

There was weak correlation of location of the tumour with histological subtype of tumour (r=0.3838, p=0.0118). Location of the tumour did not correlate with stage and tumour volume. Likewise, histological subtype did not correlate with stage and tumour volume and no correlation between stage and tumour volume (p>0.05).

DISCUSSION

Lung cancer causes 34.7 million disability-adjusted life-years [DALYs], 62% of which occurs in developing countries and 38% in developed countries. Men are more likely to develop lung cancer than women, with 1 in 18 men and 1 in 51 women being diagnosed between birth and age 79 years. In our study, 78.8% of the study populations were males. Tracheal, bronchus, and lung cancer has the second highest absolute incidence globally and in developing countries following breast cancer and fourth in developed countries following prostate, colorectal and breast cancers. It is the most common cause of cancer death by absolute cases globally as well as in developing and developed regions [10].

Non-small cell lung cancer constitutes 85-90% of all lung cancers, of which 40% are adenocarcinoma, 25-30% are squamous cell carcinoma, 10-15% are large cell carcinoma and the rest are less common varieties including adenosquamous carcinoma and sarcomatoid carcinoma.

Treatment modalities other than surgery available for non-small cell lung cancers include radiotherapy, chemotherapy, immunotherapy and targeted therapy. Targeted therapies include drugs that target the tumour blood vessel growth like bevacizumab, ramucirumab and drugs that target the cells with EGFR changes like erlotinib, geftinib, afatinib, crizotinib. Histological sub-type and stage have a major role in determining the choice of treatment. Platinum based chemotherapy is used in squamous cell carcinoma while in non- squamous sub-types, bevacizumab and targeted therapies are used depending upon the presence of specific genetic mutations in addition to platinum based chemotherapy. Radiation induced toxicity to heart, great vessels, oesophagus, spinal cord, ribs and brachial plexus depends on the location of the tumour [11]. Dose of radiotherapy is calculated from the gross tumour volume measured from anatomical imaging techniques [12].

Petralia G et al mentioned in their study that low tumour perfusion may denote a poor response to chemotherapy because delivery of chemotherapeutic agents to poorly perfused tumours is lower and low tumour perfusion also predicts a poor response to radiotherapy as poorly perfused tumours are more likely to be hypoxic resulting in poor radiosensitivity. CTP performed before starting treatment could potentially identify those patients with poorly perfused tumours who are more likely to have a poor response to chemotherapy and radiotherapy, and offer alternative or more personalized treatment regimens, avoiding expensive and ineffective treatment with potential side effects [13]. Higher

Table 6: ANOVA of permeability surface area product (PS) among different types, locations, volume and stage of the tumour.

	N	Mean	SD*	SE#	95% Confidence Interval for Mean		Minimum	Maximum	F_Value	P_Value
					Lower Bound	Upper Bound				
Type										
SCC[1]	55	25.1	12.4	1.7	21.7	28.4	6.7	64.2		
Adeno Ca[2]	21	26.0	7.4	1.6	22.7	29.4	12.8	43.5		
Adenosq Ca[3]	3	19.9	9.8	5.6	-4.3	44.2	12.4	31.0	0.248	0.863
Large cell Ca	6	24.8	15.7	6.4	8.4	41.2	5.2	44.0		
Total	85	25.1	11.4	1.2	22.7	27.6	5.2	64.2		
Location										
Central	54	25.5	11.5	1.6	22.3	28.6	7.1	64.2		
Peripheral	31	24.5	11.4	2.0	20.3	28.7	5.2	48.8	0.141	0.708
Total	85	25.1	11.4	1.2	22.7	27.6	5.2	64.2		
Volume										
>50 cm^3	62	23.4	10.4	1.3	20.7	26.0	5.2	64.2		
≤ 50 cm^3	23	29.8	12.8	2.7	24.3	35.4	9.1	57.6	5.690	0.019
Total	85	25.1	11.4	1.2	22.7	27.6	5.2	64.2		
Stage										
IV	49	24.6	12.1	1.7	21.1	28.0	5.2	64.2		
IIIB	30	24.6	10.0	1.8	20.8	28.3	7.1	43.7		
IIIA	5	32.8	12.6	5.7	17.2	48.5	15.8	48.8	0.878	0.456
IIB	1	29.7	.	.	.	.	29.7	29.7		
Total	85	25.1	11.4	1.2	22.7	27.6	5.2	64.2		

*- Standard deviation
#- Standard error
[1]Squamous cell carcinoma
[2]Adenocarcinoma
[3]Adenosquamous carcinoma

Table 7: Spearman Rank Correlation of the variables.

	AGE	BF[1]	BV[2]	MTT[3]	PS[4]	LOCATION	STAGE	TYPE	VOLUME
AGE	1.0000	0.0033	-0.0351	-0.0673	-0.0929	0.0459	-0.0046	-0.1452	0.0059
BF[1]	0.0033	1.0000	0.7873	-0.0871	0.6719	-0.1390	0.0378	0.0236	0.3589
BV[2]	-0.0351	0.7873	1.0000	0.4275	0.5793	-0.0667	0.0248	0.1143	0.1473
MTT[3]	-0.0673	-0.0871	0.4275	1.0000	0.0248	0.0364	-0.0095	0.1445	-0.2887
PS[4]	-0.0929	0.6719	0.5793	0.0248	1.0000	-0.0289	0.1119	0.0461	0.2396
LOCATION	0.0459	-0.1390	-0.0667	0.0364	-0.0289	1.0000	-0.0610	0.3838	-0.1314
STAGE	-0.0046	0.0378	0.0248	-0.0095	0.1119	-0.0610	1.0000	-0.1500	0.1660
TYPE	-0.1452	0.0236	0.1143	0.1445	0.0461	0.3838	-0.1500	1.0000	0.0326
VOLUME	0.0059	0.3589	0.1473	-0.2887	0.2396	-0.1314	0.1660	0.0326	1.0000

[1]Blood Flow
[2]Blood Volume
[3]Mean Transit time
[4]Permeability Surface area product

Table 8: Pairwise Two-sided p-values of the variables.

	AGE	BF[1]	BV[2]	MTT[3]	PS[4]	LOCATION	STAGE	TYPE	VOLUME
AGE		0.9759	0.7495	0.5403	0.3980	0.6764	0.9664	0.1848	0.9569
BF[1]	0.9759		<0.0001	0.4283	<0.0001	0.2047	0.7312	0.8299	0.0007
BV[2]	0.7495	<0.0001		<0.0001	<0.0001	0.5439	0.8215	0.2975	0.1784
MTT[3]	0.5403	0.4283	<0.0001		0.8219	0.7411	0.9311	0.1870	0.0074
PS[4]	0.3980	<0.0001	<0.0001	0.8219		0.7930	0.3080	0.6752	0.0272
LOCATION	0.6764	0.2047	0.5439	0.7411	0.7930		0.5794	0.0003	0.2307
STAGE	0.9664	0.7312	0.8215	0.9311	0.3080	0.5794		0.1706	0.1288
TYPE	0.1848	0.8299	0.2975	0.1870	0.6752	0.0003	0.1706		0.7672
VOLUME	0.9569	0.0007	0.1784	0.0074	0.0272	0.2307	0.1288	0.7672	

[1]Blood Flow
[2]Blood Volume
[3]Mean Transit time
[4]Permeability Surface area product

Table 9: Adjusted p-values (Holm's Method) of the variables.

	AGE	BF[1]	BV[2]	MTT[3]	PS[4]	LOCATION	STAGE	TYPE	VOLUME
AGE		1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
BF[1]	1.0000		<0.0001	1.0000	<0.0001	1.0000	1.0000	1.0000	0.0298
BV[2]	1.0000	<0.0001		0.0019	<0.0001	1.0000	1.0000	1.0000	1.0000
MTT[3]	1.0000	1.0000	0.0019		1.0000	1.0000	1.0000	1.0000	0.2800
PS[4]	1.0000	<0.0001	<0.0001	1.0000		1.0000	1.0000	1.0000	1.0000
LOCATION	1.0000	1.0000	1.0000	1.0000	1.0000		1.0000	0.0118	1.0000
STAGE	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000		1.0000	1.0000
TYPE	1.0000	1.0000	1.0000	1.0000	1.0000	0.0118	1.0000		1.0000
VOLUME	1.0000	0.0298	1.0000	0.2800	1.0000	1.0000	1.0000	1.0000	

[1]Blood Flow
[2]Blood Volume
[3]Mean Transit time
[4]Permeability Surface area product

perfusion values in tumours reflect the process of angiogenesis, with the recruitment and development of arteriovenous shunts, dilated capillary beds and hyperpermeable vessels. These result in high values of blood flow, blood volume and permeability which are measured with CTP. Fraioli et al [14] and Wang et al [15] found significant differences in perfusion parameters before and after therapy and thereby helping in response prediction. The former study showed higher BF and PS values and latter study showed higher BF and BV values in responders than in non-responders. Similar results have been found not only in lung cancer, but also in rectal [16] and head and neck malignancies [17].

In this study, various characteristics of non-small cell lung cancer found in histopathology and in anatomical imaging studies which have relevance in the choice of treatment were compared with the perfusion parameters measured by CT perfusion prior to initiation of therapy which gives an idea about the tumour microenvironment.

In our study, CTP was done in 64 slice MDCT scanner with

volume helical shuttle. Z-axis coverage was 14cm. Hence the entire tumour was covered in all the patients in our study and therefore we could assess the tumour perfusion for the whole tumour. The maximum z-axis coverage mentioned in literature till now is by Fraioli et al [14] where a scanning range of 136mm was used. It has been shown thattumour perfusion measurement reproducibility improves with greater *z*-axis coverage [4].

The duration of scanning of CTP in our study was 40 seconds and it was performed in a single phase. Spira D et al [18] assessed the effect of measurement time on perfusion with different measurement times. The study found that estimation of BF in lung cancer was independent from CTP measurement time whereas both BV and k-trans were affected by measurement duration. They recommended a fixed measurement time of 40 seconds. Ng C S et al [19] found that perfusion parameters derived from deconvolution modeling can be markedly affected by time of acquisition and pre-enhancement set-points. 50s acquisition may be adequate for BV, but longer than 125 s is probably required for reliable characterization of the other three perfusion parameters [BF, MTT, PS]. Based on the data available in literature and considering the radiation dose to the patients, acquisition was done in a single phase in our study.

There was no separate motion correction technique available in our scanner and processing software. The patients were demonstrated how to breathe in a constant and calm manner and rehearsed well before the procedure. And then CTP was performed in quiet calm breathing to reduce motion related artefacts as it is not possible to hold breath for 40 seconds. Fraioli et al [14] also used a free breathing dynamic acquisition and all patients were instructed to breathe in a constant manner to avoid excessive lung motion that may hamper post processing and prolong image evaluation. Ng C S et al [19] found that the absolute values and reproducibility of perfusion parameters in lung tumours are markedly influenced by motion and duration of data acquisition. The impact of motion on perfusion parameter values is likely because of the possibility of rapid changes in Hounsfield density that might occur within pixels when movement is encountered. A sudden change from the very low densities of normal lung parenchyma to those of adjacent tumour soft-tissue density would give the artefactual impression of rapid inflow of contrast agent. In our study, images were never hampered by motion artefacts.

There was statistically significant difference in BF, MTT and PS values in >50 cm^3 and ≤50 cm^3 tumour volume groups [p= 0.001, 0.021 and 0.019 respectively], with higher BF and PS values in ≤50 cm^3 tumour volume group and higher MTT value in >50 cm^3tumour volume group in our study. Also there was weak positive correlation of BF value with volume of tumour. It had been previously shown by Miles et al [20] and Kiessling et al [21] that perfusion parameters particularly BF depended on tumour dimensions. Kiessling et al also found that tumours with larger volumes showed a significantly lower perfusion than the smaller ones [p = 0.001] and explained the reasons that the development of central tumour necrosis and the increasing interstitial pressure secondarily lowers the perfusion in the peripheral, high enhancing areas in larger tumours. Our study also support this theory as we measured perfusion parameters only on the enhancing parts of the tumour and the necrosed centre was not included in the measurement. Li Y et al [22] also showed that tumour perfusion decreased with increasing sizes. As tumours increase in size, they may out-grow their blood supply and then get necrosed. They found that necrotic tumours exhibited significantly lower perfusion, peak enhancement image (PEI) and BV than those of non-necrotic tumours. Furthermore, perfusion, PEI and BV of necrotic part were also considerably lower than those of non-necrotic portion of necrotic tumours. These findings suggested that necrosis might be one of the important intrinsic factors influencing tumour perfusion.

There is differential perfusion of the lungs due to factors such as gravity and patient position. Also tumour receives its blood supply by recruiting vessels from neighbouring tissues and the extent of recruitment in turn depends on the location of the tumour. Central tumours receive lesser perfusion due to lower blood vessels area fraction in the central lung tissue. However, in our study, no valid information could be demonstrated from perfusion values with respect to tumour location. Ovali et al [23] and Huellner et al [24] also found no statistically significant difference in perfusion parameters between central and peripheral tumours in their studies. Location of the tumour did not correlate with any of the perfusion parameters. Other than weak correlation with histological subtype, location of the tumour had no effect on the stage of tumour and no association with volume of the tumour in our study.

There was no significant difference in perfusion values among various stages. However, BV and BF values increased with advancing stage and dropped in Stage IV while MTT values decreased with advancing stage and increased in Stage IV. Stage of the tumour correlated neither with the perfusion values nor with histological sub-type, location or volume of tumour. In the study by Ovali et al [23] BF values were lower in tumours with distant metastasis than in locally advanced tumours. Li Y et al [25] found no statistically significant differences between nodule metastasis positive and negative groups ($p > 0.05$). In our study, mean PS value was same in both locally advanced (Stage IIIB) and distant metastatic (Stage IV) groups. PS stands for permeability surface area product which represents the leakiness of the newly formed tumour vessels by "neoangiogenesis". Hence, mere presence of neoangiogenesis is not sufficient for the development of metastasis. It involves a complex interaction of other factors such as the angiolymphatic invasion, adhesion molecules, and immunologic mechanism for the development of metastasis which may not be identified by perfusion parameters alone. Another study by Zhou et al [26] found that low blood flow in T1b tumours predicted lymph node metastasis. In our study, all patients had lymph node metastasis and were of advanced T stage. Hence, no such correlation could be made between perfusion values and stage of tumour.

Number of studies with mixed results had been published till now in utilising perfusion parameters measured by CTP as an aid in differentiating various histological sub-types of lung cancer [21-23,27]. In this study, the perfusion parameters were not statistically different among various histological sub-types. However, BV and BF values were higher in adenocarcinoma than in squamous cell carcinoma. Also, histological sub-types

had weak correlation with location of the tumour and did neither correlate with perfusion parameters nor with stage and volume of the tumour. In the study by Shi J et al [27], there was significant difference in PS value among SCC, adenocarcinoma and small cell lung cancer. There was no difference in BV and BF values between SCC and adenocarcinoma. Ovali et al [23] found significant difference in BF values and but they were higher in SCC than in adenocarcinoma. In the study by Li Y et al [25] comparing microvessel density (MVD) with histological sub-type, MVD was more intense in adenocarcinoma than in SCC. BV and BF values correlate with MVD which might be the reason for higher BF and BV values in adenocarcinoma than in SCC.

With the emergence of novel targeted therapies as a promising strategy in cancer, techniques like CTP that assess tumourvascular support have gained credence for response assessment alongside standard response criteria (RECIST 1.1) [28]. Agents targeted at the tumourvasculature may have considerable antivascular effect and clinical benefit is underestimated by size change alone due to their cytostatic rather than cytoreductive nature. Marked reduction in tumourenhancement may occur without significant size change [8]. In our study, perfusion parameters showed good correlation as well as seemed dependent on the volume of the tumour. Hence, CTP may be useful if done prior to initiation of non-surgical treatment. CTP may be done along with conventional anatomical imaging studies to monitor treatment and detect early response to treatment.

Our results need to be confirmed on a larger cohort of patients. The perfusion parameters measured in our study were based on the deconvolution algorithm present in our software. Goh V et al [29] compared the level of agreement between perfusion parameters measured using adiabatic approximation of distributed parameter analysis and Patlak analysis. They found disagreement between the methods used to estimate tumour vascularity and concluded that measurement techniques were not directly interchangeable.

CONCLUSION

CT perfusion done prior to initiation of therapy revealed significant correlation within perfusion parameters and also with tumour volume. Perfusion parameters may be related to tumour volume. No valid information could be found by perfusion parameters with respect to different histological sub-types, stage and location of tumour. CTP may be done prior to initiation of non-surgical treatment along with routine conventional contrast enhanced CT/MR of thorax to monitor treatment and assess response complementing RECIST which is based on measurement of size alone.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63:11-30.
2. Srinivasan A, Mohan S, Mukherji SK. Biologic Imaging of Head and Neck Cancer: The Present and the Future. AJNR Am J Neuroradiol. 2012; 33:586 – 94.
3. Miles KA, Hayball MP, Dixon AK. Functional images of hepatic perfusion obtained with dynamic computed tomography. Radiology. 1993; 188: 405–411.
4. Lee SM, Lee HJ, Kim JI, Kang MJ, Goo JM, Park CM et al. Adaptive 4D Volume Perfusion CT of Lung Cancer: Effects of Computerized Motion Correction and the Range of Volume Coverage on Measurement Reproducibility. AJR Am J Roentgenol. 2013; 200: 603-609.
5. Miles KA. Perfusion CT for the assessment of tumour vascularity: which protocol? Br J Radiol 2003; 76: 36–42.
6. 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: 165–177.
7. Ng QS, Goh V. Angiogenesis in Non-small Cell Lung Cancer Imaging With Perfusion Computed Tomography. J Thorac Imaging. 2010; 25:142-150.
8. Miles KA. Functional computed tomography in oncology. Eur J Cancer. 2002; 38: 2079-2084.
9. American Joint Committee on Cancer. Lung. AJCC Cancer Staging Manual. 7th ed. New York: Springer. 2010: 253–266.
10. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D. The Global Burden of cancer 2013. JAMA Oncol. 2015; 1: 505-527.
11. Kong F-M [Spring], Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: Atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J radiation oncology, biology, physics. 2011; 81: 1442-1457.
12. Burnet NG, Thomas SJ, Burton KE. Defining the tumour and target volumes for radiotherapy. Cancer Imaging. 2004; 4: 153-161.
13. Petralia G, Bonello L, Viotti S, Preda L, Andrea D, Bellomi M. CT perfusion in oncology: how to do it. Cancer Imaging. 2010;10: 8-19.
14. Fraioli F, Anzidei M, Serra G. Whole-tumour CT-perfusion of unresectable lung cancer for the monitoring of anti-angiogenetic chemotherapy effects. Br J Radiol. 2013; 86: 20120174.
15. Bellomi M, Petralia G, Sonzogni A, Zampino MG, Rocca A, et al. CT perfusion for the monitoring of neoadjuvant chemotherapy and radiation therapy in rectal carcinoma: initial experience. Radiology. 2007; 244: 486–493.
16. Hermans R, Meijerink M, Van den Bogaert W et al. Tumor perfusion rate determined noninvasively by dynamic computed tomography predicts outcome in headand-neck cancer after radiotherapy. Int J Radiat Oncol Biol Phys. 2003; 57: 1351–1356.
17. Spira D, Gerlach JD, Spira SM, Schulze M, Sauter A, Horger M, et al. Effect of Scan Time on Perfusion and Flow Extraction Product [K-Trans] Measurements in Lung Cancer Using Low-Dose Volume Perfusion CT [VPCT]. Acad Radiol. 2012; 19: 78–83.
18. Ng CS, Chandler AG, Wei W, Anderson EF, Herron DH, Charnsangavej C, et al. Reproducibility of Perfusion Parameters Obtained From Perfusion CT in Lung Tumors. AJR Am J Roentgenol. 2011; 197: 113–121.
19. Miles KA, Griffiths MR, Keith CJ. Blood flow-metabolic relationships are dependent on tumour size in non-small cell lung cancer: a study using quantitative contrast-enhanced computer tomography and positron emission tomography. Eur J Nucl Med Mol Imaging. 2006; 33: 22-28.
20. Kiessling F, Boese J, Corvinus C, Ederle IZ, Schoenberg SO, Brix G, et al. Perfusion CT in patients with advanced bronchial carcinomas: a novel chance for characterization and treatment monitoring? Eur Radiol. 2004; 14:1226–1233.
21. Li Y, Yang ZG, Chen TW et al. Whole tumour perfusion of peripheral lung carcinoma: evaluation with first-pass CT perfusion imaging at

64-detector row CT. Clin Radiol. 2008; 63: 629-635.

22. Ovali GY, Sakar A, Goktan C, Celik P, Yorgancıoglu A, Nese N, et al. Thorax perfusion CT in non-small cell lung cancer. Comput Med Imaging Graph. 2007; 31: 686–691.

23. Huellner MW, Collen TD, Gut P, Winterhalder R, Pauli C, Diebold J, et al. Multiparametric PET/CT-perfusion does not add significant additional information for initial staging in lung cancer compared with standard PET/CT. EJNMMI Research. 2014; 4: 6.

24. Li Y, Yang ZG, Chen TW, Chen HJ, Sun JY, Lu YR. Peripheral lung carcinoma: Correlation of angiogenesis and first-pass perfusion parameters of 64-detector row CT. Lung Cancer. 2008; 61: 44-53.

25. 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 Canc. 2013; 4: 131-137.

26. Shi J, Schmid-Bindert G, Fink C, Sudarski S, Apfaltrer 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: 894-900.

27. Eisenhauer E A, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45: 228–247.

28. Goh V, Halligan S, Bartram CI. Quantitative Tumor Perfusion Assessment with Multidetector CT: Are Measurements from Two Commercial Software Packages Interchangeable? Radiology. 2007; 242: 777-782.

Cite this article

Venkat B, Sharma S, Aggarwal N, Sankaran M, Sharma D, et al. (2018) Whole Tumour CT Perfusion in Non-Small Cell Lung Cancer: Evaluation of Perfusion Parameters Prior to Initiation of Therapy. JSM Clin Med Imaging Cases Rev 3(1): 1011.