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Original Article

Role of Perfusion Computed Tomography in the Characterization of Lung Cancers

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Abstract
Purpose: *Aim of our study is the evaluation of CT perfusion parameters in lung cancers according to their histopatholgical subtypes, size, location and necrosis.*
Method and Materials: *We performed CT perfusion in 28 patients of lung cancers on 128 slice CT scanners and calculated blood flow (BF), blood volume (BV), permeability (PMB) and mean transit time (MTT).*
Statistical Analysis: *Depending on the distribution of data, unpaired t-test and Mann Whitney U test were used to compare CT perfusion parameters of lung cancers. P value <0.05 was accepted statistically significant.*
Results: *Histology revealed squamous cell cancer (SCC) in 16 patients, adenocarcinoma (Adeno) in 10 patients and small cell lung cancer (SCLC) in 2 patients. We found that BF and PMB were significantly higher in Adenocarinoma than SCC (p <0.05). BV and MTT were not significantly differ according to lung cancer subtypes (p>0.05). Tumour of less than 3 cm in size showed significantly higher BF and PMB than tumour size greater than 3 cm (p<0.05). CT perfusion parameters were not significantly differ according lung cancer location (central versus peripheral and upper lobe versus lower lobe). BF, PMB and MTT were found significantly different between non-necrotic tumour and necrotic tumour (p<0.05).*
Conclusions: *In conclusion, CT perfusion parameters of lung cancer using 128-multi-detector row CT could reflects the underlying extent of tumour angiogenesis in relation to lung cancer subtypes, size and necrosis.*
Keywords: *Lung cancer, perfusion CT, Tumour angiogenesis.*

Introduction

Lung cancer represents the leading cause of cancer related death world-wide and majority of patients with lung cancer already suffer from advanced stages of the disease at time of initial diagnosis.[1] These patients are not suitable for curative surgery, and are treated with chemotherapy, radiotherapy, radio-chemotherapy and recently developed novel anti-angiogenic drugs.[2]

Tumour angiogenesis is currently a leading theme in oncology because it is critical for tumour growth, invasion and metastasis.[3,4] Now, the increased use of drugs targeting angiogenic pathways in lung cancer is drawing attention to a reliable non-invasive assessment of tumour vascular characteristics through imaging hoping for early detection, staging of tumour as well as prognostic biomarkers that may aid in tailoring treatment regimens.

Perfusion CT is a promising modality for non-invasive in-vivo assessment of tumour vascularity.[5] Due to the wider availability, faster scanning times and low cost , as a non-invasive technique perfusion CT can be readily incorporated into patient's routine CT examination for lung cancer evaluation, and functional information can be obtained by reflecting hemodynamic changes in addition to anatomical details.

Thus, aim of our study was the evaluation of CT perfusion parameters in lung cancers using 128 slice CT scanner according to their histopatho-logical subtypes, size, location and necrosis.

Materials and Methods

This prospective study was approved by the institutional ethics committee and informed consent was obtained from all patients prior to enrolment in the study.

Between January 2015 and January 2016, consecutive 34 patients (mean age 57.6 years, range 40 to 84 years) with clincoradiologically suspected lung cancer were enrolled in the study. CT perfusion was performed in all patients. Patients were selected for final analysis according to the following criteria – (1) histopathologically proven primary lung cancer, (2) No prior chemotherapy or radiotherapy for the lung cancer (3) No contraindication to contrast administration. Six patients were excluded after the scan because two patients showed marked respiratory motion artifacts and histology results revealed benign lesions in rest of four patients. Thus, total 28 patients (24 males and 4 females) of primary lung cancers were finally analyzed in our study.

CT Perfusion imaging technique

All examinations were performed on 128 slice CT scanner (Siemens Somatom Definition AS, Siemens Healthcare Sector, Germany). Firstly, non-enhanced CT (NCCT) of thorax was performed for localization of tumour. (kV80, mAs 40-100). Subsequently, perfusion CT was then performed through the area of interest (maximum span 9.6 cm along z-axis) using a dedicated perfusion protocol combining a cine CT acquisition with simultaneous intravenous injection of contrast. 50 ml of low osmolar non-ionic contrast (350 mg/ml) was injected at a rate of 5 ml/s followed by 30 ml of saline chase with same rate using a dual head pressure injector (Medrad). Multiphase dynamic CT acquisition of the region of interest was started 2 seconds after the beginning of injection of the contrast, lasting for approximately 60 seconds during which the patient was instructed to breathe gently to minimise respiratory excursion, using the following parameters 80kV, automated tube current modulation, 0.3s rotation time and 512x512 mm matrix. In case of more than one pulmonary tumour, the largest suspected primary tumour was chosen for the perfusion CT. Subsequently, contrast-enhanced CT (CECT) of chest was also obtained.

Image Analysis

The conventional NCCT and CECT images were evaluated to characterize the lesion size, location, necrosis. Longest diameter was taken on lung window settings.

The dynamically acquired images were then analysed. The acquired data was loaded on to a separate workstation with dedicated CT perfusion software (Syngo volume perfusion body CT). Dynamic perfusion CT data was corrected for motion with an integrated registration technique. The degrading images, if any were excluded from the subsequent evaluation. An arterial input was then defined by using a circular region of interest marked within descending thoracic aorta or its branches on the selected image depending on the location of the lesion. The software automatically derived a smoothed arterial time- enhancement curve and perfusion maps were generated.

To evaluate the perfusion parameters of lesion, the region of interest (ROI) was placed manually within the lesion in the enhancing area for each contiguous axial section of entire tumour. Then a global value representing the perfusion of the entire tumour was calculated by taking the mean value of all individual sections involved. Care was taken to exclude surrounding air, atelectatic lung, intra-tumoural calcification. A tissue enhancement curve and the perfusion parameters were derived automatically for the selected region of interest. The following CT perfusion parameters were evaluated: Blood flow (BF) in ml/100g/min, which represents flow rate through vasculature in tissue region. Blood volume (BV) in ml/100g, which indicates volume of flowing blood within a vasculature in tissue region. Permeability(PMB) in ml/100g/min, which indicates total flux from plasma to interstitial space. Mean transit time (MTT) in seconds, which indicates average time taken to travel from artery to vein.

Histopatholgical Analysis

All the patients underwent either image guided or bronchoscopic guided biopsy depending on the location of lesions.

Statistical Analysis

All statistical analyses were performed using commercially available software SPSS v 16.0 for Windows. All data were expressed as means ± standard deviation (S.D). The Shapiro- Wilks normality test was used to determine whether measurable variables showed normal distribution. Depending on the distribution of data, Unpaired t-test and Mann Whitney U test were used to compare CT perfusion parameters of lung lesions of our study according to their histological subtypes, size, location and necrosis. p-value <0.05 was accepted statistically significant.

Results

Of these 28 patients (24 males and 4 females), the majority were diagnosed with non-small cell lung cancer (NSCLC; n=26), and two patients with small cell lung cancer (SCLC; n=2). Among NSCLC, 16 patients were squamous cell carcinoma (SCC; n=16) and 10 patients were adenocarcinoma (AC; n=10).

CT Perfusion parameters in different subtypes of lung cancer

Between NSCLC and SCLC, BF and PMB were higher in NSCLC, but it was not statistically significant (p = 0.068 & p =0.95 respectively).

Among NSCLC, Adenocarcinoma showed significantly higher BF and PMB than SCC (p = 0.001 & p =0.049), however no significant difference seen in BV and MTT (p =0.071 & p =0.36 respectively). (Table 1)

Location of Lung Cancer and Perfusion Parameters

Central tumour was defined as having contact to the hilum, whereas all other tumours were considered peripheral.[6] All SCLC were centrally located (2/2 i.e. 100%), whereas SCC (11/16 i.e.68.75%) and Adenocarcinoma (7/10 i.e. 70%) were found predominantly in peripheral location. BF and PMB were found to be significantly higher in peripheral tumour than central tumour (p<0.05). However no significant differences of perfusion parameters were found in relation location of tumour between upper lobes and lower lobes (p>0.05). All data were mentioned in table 2.

Tumour size and perfusion parameters

Perfusion values according to tumour size are summarized in table.3. The mean BF and PMB were significantly higher in lung cancer of size <3cm in comparison to tumour of >3cm ($p<0.05$), whereas MTT was found significantly in larger tumour (>3cm) ($p<0.05$).

Tumour necrosis and Perfusion Parameters

Table.3 summarized the perfusion values and the mean BF and PMB were found higher in non-necrotic lung cancer than necrotic ones (p~, whereas mean MTT was noted higher in necrotic cancer and these differences were found to be statistically significant ($p<0.05$).

Table1. Perfusion parameters in Lung cancer subtypes

Perfusion Parameters	NSCLC		SCLC (mean ±SD)
	SCC (mean ± SD)	ADENO CA (mean ± SD)	
BF (ml/100ml/min)	59.21± 5.45	74.40 ± 13.13	55.3 ± 2.68
BV (ml/100ml)	11.46 ± 3.35	15.88 ± 7.73	10.92 ± 2.0
PMB (ml/100ml/min)	23.03 ± 6.41	31.14 ± 10.69	21.78 ± 2.0
MTT (seconds)	10.24 ± 4.16	8.52 ± 3.82	9.3 ± 7.21

Table 2 Location of tumours and perfusion parameters

Location	BF	BV	PMB	MTT
Central (n=10)	60.93 ± 12.22	12.9 ± 4.0	22.69 ± 5.53	9.84 ± 3.41
Peripheral (n=18)	66.43 ± 11.50	13.06 ± 6.40	27.55 ± 9.9	9.40 ± 4.57
Upper lobe (n=23)	62.56 ± 9.78	11.93 ± 3.54	25.62 ± 7.82	9.86 ± 4.26
Lower lobe (n=5)	73.25 ± 17.42	17.95 ± 10.19	26.84 ± 13.58	8.16 ± 3.48

Table 3 CT perfusion parameters in accordance to tumour size and necrosis

Perfusion parameters	Tumour ≤3cm (n=6)	Tumours> 3cm (n=22)	Non-necrotic tumour (n=11)	Necrotic tumour (n=17)
BF	75.91±12.62	61.34±9.74	71.77±12.97	59.74±8.44
BV	16.7±9.65	11.99±3.59	15.12±7.61	11.36±3.35
PMB	36.76±10.37	22.85±5.52	31.61±9.37	22.09±5.80
MTT	6.72±3.24	10.33±4.0	6.5±2.8	11.54±3.65

Figure 1 CT perfusion map of peripherally located Adenocarcinoma showing the distribution of perfusion within the tumour is heterogeneous. The color spectrum indicates the value of the perfusion parameters, ranging from high (red) to low (violet).

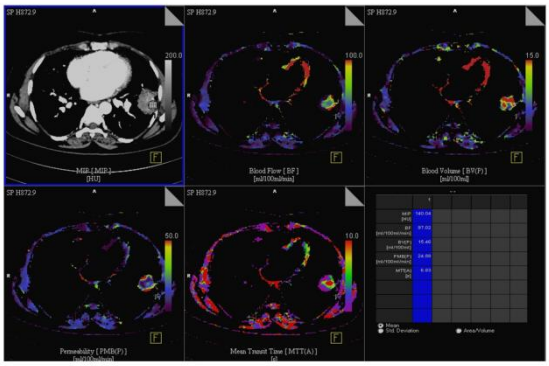
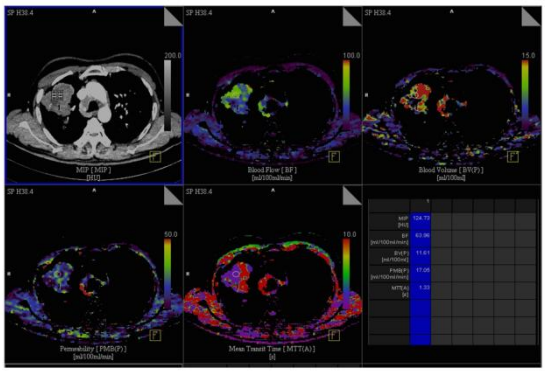


Figure 2 Perfusion CT images of peripherally located Squamous Cell carcinoma. The necrotic area appears violet on perfusion maps suggesting very low perfusion, whereas solid enhancing area stand out as yellowish-green on perfusion map.



Discussion

Conventional contrast enhanced CT is an established tool in evaluating lung cancer, but it provides only anatomical and structural evaluation of lesion. The study of tumour biology is at frontline of oncology research; in particular, neoplastic angiogenesis is considered to be an important prognostic factor and promising target of new anti-angiogenic tumour therapies in lung cancer. The recent availability of commercial software that enables existing CT systems to capture physiological parameters reflecting the

vasculature (angiogenesis) within tissues by applying mathematical models has heralded the arrival of CT perfusion into clinical arena.[7]

In this study, we found that adenocarcinoma of lung appeared the most vascular among the three most prevalent subtypes of lung cancers (i.e. adenocarcinoma, squamous cell carcinoma, small cell lung carcinoma). The mean BF, BV and permeability (PMB) were found highest in adenocarcinoma followed by squamous cell carcinoma and small cell lung cancer, whereas the mean MTT was noted highest in small cell lung cancer, followed by squamous cell carcinoma and adenocarcinoma. Similar to our findings, Shi J et al who evaluated perfusion in lung cancer on 128 slice CT scanner, found that highest BF, BV and PMB were seen in adenocarcinoma followed by SCC and SCLC.[8] Similarly, Spira D et al also reported highest BF and PMB in adenocarcinoma followed by SCC and SCLC.[9] In partial agreement to our study, previous few authors observed the highest BF in adenocarcinoma; however SCLC showed higher BF than squamous cell carcinoma.[10,11] In contrast to our study, Ovali G Y et al observed higher BF in squamous cell carcinoma than adenocarcinoma in perfusion study using single slice CT scanner.[12]

In present study, among non-small cell lung cancer (NSCLC), the mean BF and PMB were found significantly higher in adenocarcinoma in comparison to SCC ($p<0.05$). However BV and MTT were not significantly differed between adenocarcinoma and SCC. In agreement to our study, Shi J et al found significantly higher permeability in adenocarcinoma than SCC ($p<0.05$), however they found no significant difference of BF, BV and MTT between these two subtypes of lung cancer.[8] Several previous studies found higher perfusion (BF &BV) and lower MTT in adenocarcinoma than SCC and these differences were not significant. In contrast to our findings, Ovali GY et al found significantly higher BF in SCC than adenocarcinoma.[12] The differences in value of perfusion parameters observed in our study when compared to other studies may be due to difference in dosage, software and mathematical model used in analysis and small sample size. Goh et al in his review article suggested that cross study comparison would be problematic if variation between techniques was not taken into account.[13] They advocated standardization of analysis method and software implementation and a cautious approach to data interpretation until standardization was achieved.

The tumour size is one of the main determinants of the tumour stage and therapeutic management. In our study, we divided the total lung cancers in two groups according to size: tumours of ≤ 3cm and tumours of > 3cm in accordance to TNM staging (T1 ≤3cm and T2 >3cm). We found that the mean BF and mean permeability or PMB were found to be higher in the lung tumours ≤ 3cm in size in comparison to the tumour of > 3cm in size and these differences were found statistically significant ($p= 0.036$, & $p = 0.02$ respectively), while MTT was found to be significantly higher in lesions of diameter >3 cm when compared to tumours of ≤3cm ($p=0.039$). Although the mean BV was noted to be higher in tumour ≤3cm in size than larger tumour >3cm in our study, it was not statistically significant difference ($p=0.194$). Similar to our study, Ippolito D et al found significantly higher BF in tumour of ≤ 3cm than tumour > 3cm, while significantly lower MTT was found in small tumour.[14] Keisling et al. and Li Y et al. also observed significantly higher perfusion in smaller tumours than larger one.[6,15] Several mechanisms have been advocated to explain why large tumours are poorly vascularized and have a poor prognosis. The decrease in micro vessel density (MVD) reflects the inability of tumour neovascularization to support the fast proliferation of the tumour cells, leading to a reduced vascular supply, resulting in necrosis, which is very frequent in larger lesions. In addition, development of necrosis and fibrosis are frequently observed in large tumours, which may be cause of lower perfusions. These variations of perfusion parameters in relation to the size of lung

cancer might be due to underlying tumour angiogenesis and these findings could contribute valuable information for angiogenic therapeutic approach in lung cancer

The mean BF, BV and PMB were also found higher in peripheral lung cancer in comparison to central tumour, however these difference were not statistically significant. (p=0.79 & p=0.1 respectively). The mean MTT was found to be higher in centrally located lung cancer than peripherally located cancer and it was also not statistically significant (p=0.68). These findings were in agreement with those observation made by earlier authors who found higher perfusion parameters in peripherally located tumours which were not statistically significant.[9,11] In contrast, Keisling et al. and Yildrim I.O. et al. found significantly higher perfusions in peripheral tumours than centrally located lung cancer.[6,10] One study made by Ovali G Y et al observed higher perfusion parameters in central cancer than peripheral lung cancer using one slice CT scanner and however these difference were not significant.[12]

We found that the mean BF, BV and PMB higher in lower lobe lung cancers in comparison to upper lobe lung cancers, however these differences were not statistically significant (p >.05), whereas the mean MTT was lower in lower lobe tumours than upper lobe and it was also not significant. Previous two studies observed similar findings.[9,14] The difference in values of perfusion parameters in relation to the location of lung tumors in comparison to other previous studies could be due to relative small number of cases in our study but more importantly can also be attributed due to difference in software analysis, variations in the perfusion protocol, technique and CT scanner used in the various studies as discussed earlier. There are hypothesis that gravity and patient position have an impact on lung perfusion. However, in the present study, no perfusion differences related to location could be substantiated.

In our present study, the mean BF and PMB values were found higher in non-necrotic (solid) malignant lung tumour in comparison to necrotic tumour of lung, whereas the mean MTT was noted higher in necrotic tumour than solid one and these differences were found statistically significant (p<0.05). Although the mean BV was higher in non-necrotic lung cancer in comparison to necrotic tumour, the difference was not statistically significant (p=.136). These findings are in accordance with observation of Yildrim I.O. et al who found significantly lower BF and higher MTT in necrotic lung cancer in comparison to solid one (p<0.05).[10] The author also found significantly higher BV in solid tumour than necrotic tumour in contrast to our finding. Li Y et al also reported lower perfusion, PEI (peak enhancement intensity) and BV in necrotic lung cancer in comparison to non-necrotic tumours.[15] As tumours increase in size, they may out-grow their blood supply with resultant necrosis which has been already discussed earlier. This may be the cause of lower perfusion in necrotic tumours. However, these findings of different perfusion parameters in necrotic and non-necrotic tumour suggested that necrosis might be one of the important intrinsic factors influencing tumour perfusion, especially in fast-growing lung cancers, and it might have a potential role as an indicator for therapeutic monitoring of lung carcinoma following radiotherapy or chemotherapy.

A crucial issue related to perfusion CT concerns the dose of radiation delivered to the patient. In a study published by Dominik K et al observed that mean radiation dose of perfusion CT for thorax covering 6.9cm tumor along z-axis was between 3.5 mSv to 6.5 mSv using fixed 80 kV, 60 mAs/ 80mAs depending on patient's age and weight on 128 slice single source scanner (SOMATOM DEFINITION AS+ Siemens).[16] Similarly, fixed lower tube setting of 80 kV with automatic tube current modulation was set in the dynamic scan of our study to decrease radiation dose. Also we have to be aware that the radiation dose delivered during this perfusion CT study is much smaller than those given during radiotherapy for lung cancer.

Limitations of Our Study

We acknowledge some limitations in our study. First, the sample size of our study was very small especially small cell carcinoma and we had not even a single large cell lung cancer patient. Data from a larger patient population with various types of primary lung carcinoma are needed in future studies. Second, the observational period was relative short, so the clinical outcomes based on perfusion parameters obtained using dynamic CT could not be analysed. Thirdly, we did not analyze perfusion parameters of lung cancer according to staging.

Conclusion

In conclusion, 128-multi-detector row CT perfusion imaging offers a rapid, easy and non-invasive option in the evaluation of tumour perfusion in patients with lung carcinoma and CT perfusion parameters could reflect the underlying extent of tumour angiogenesis in relation to lung cancer subtypes, size and necrosis. However, it should be emphasized that the results of our study are specific to the analytical methods and software employed. Further studies investigating the role of perfusion CT in characterization of lung cancers along with its prognostic value are necessary in a larger number of patients.

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