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The evaluation of MDCT and quantitative first-pass perfusion in lung cancers

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Abstract. – OBJECTIVES: The aim of this study was the in vivo evaluation of tumor angiogenesis in lung cancers grouped according to their histopathological diagnosis, localization and necrosis characteristics determined using CT first-pass parameters.

MATERIALS AND METHODS: The study was performed between January and April 2012 on 44 patients consisting of 38 males and 6 females who were diagnosed with lung cancer as a result of cytological and/or histopathological evaluations. Patients who had not received radiotherapy and/or chemotherapy previously were included in the study. Images were obtained for each patient by using the 64-detector MDCT scanner. Colored perfusion maps were created from the obtained images. Perfusion parameter measurements were performed by placing ROI at 3 different locations in the solid sections, avoiding the necrotic cystic areas of the masses. Obtained BV, BF, TTP, and MTT perfusion parameters were recorded.

RESULTS: The BF values of central and peripherally located lung cancers that showed normal distribution were found to be statistically significantly different. No statistically significant difference was found between TTP values. The BV values of central and peripherally located lung cancers that did not show normal distribution showed a statistically significant difference. There was a statistically significant difference between the BV and BF values of lung cancer with and without necrosis that did not show a normal distribution and the BV and BF values of lung cancers with and without necrosis.

CONCLUSIONS: Non-invasive evaluation of tumor perfusion of first-pass perfusion CT in lung cancers provides valuable information about tumor angiogenesis. However, we believe that peripheral and solid lung cancers will benefit more from treatments such as anti-angiogenetic drugs, radiotherapy and chemotherapy more than the centrally located and necrotic lung cancers and that perfusion CT will play a greater role in the evaluation of the efficiency of these treatments in the future.

Key Words:
First-pass perfusion CT, Lung cancers.

Abbreviations

CT = Computed Tomography; MDCT = Multidetector Computed Tomography; ROI = Region of Interest; BV = Blood Volume; BF = Blood Flow; TTP = Time to Peak; MTT = Mean Transit Time; PS = Permeability Surface Area Product of Volume; SCLC = Small Cell Lung Cancer; NSCLC = Non-Small Cell Lung Cancer; MVD = Microvascular Density; PEI = Peak Enhancement Intensity; SPN = Solitary Pulmonary Nodule; FDG = Fludeoxyglucose; TNM = Tumor, Node, Metastasis; VEGF = Vascular Endothelial Growth Factor.

Introduction

Lung cancers currently rank first in cancer-related deaths. The widespread use of MDCT provides many advantages in lung cancer diagnosis and staging compared to spiral CT[1]. Perfusion CT enabling functional evaluation of tissue vascularity is also in common use with MDCT in recent years. The clinical use of perfusion CT in head-neck, lung, liver, pancreas, colorectal and prostate cancer has been reported[2].

The aim of this study was the *in vivo* evaluation of tumor angiogenesis in lung cancers grouped according to their histopathological diagnosis, localization and necrosis inclusion characteristics by using first-pass perfusion CT parameters. The data obtained is thought to provide valuable information in the follow-up of lung cancers and in the evaluation of the efficiency of anti-angiogenetic drugs used in the treatment.

Materials and Methods

The study was performed between November 2011 and April 2012 on 44 patients consisting of 38 males and 6 females who were diagnosed with lung cancer as a result of cytological and/or histopathological evaluations. The mean age of

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the cases was 64.1 (44-80) years. Patients who had not received radiotherapy and/or chemotherapy previously were included in the study. Six patients with respiratory motion artifact and not suitable for the imaging protocol were excluded and our study was completed with 44 patients.

CT Technique

A 64-detector MDCT scanner (Aquillion 64 Model TSX-101A, Toshiba Medical Systems, Tochigi Japan Corporations, Tochigi, Japan) was used in each patient using the following parameters: kVP, 120; mA, 70; msec, 1000; thickness, 8 mm. Then, scout and standard non-contrast images were primarily obtained. Sections that included mass were determined from the obtained images. A total area of 3.2 cm was screened along the Z axis. After determining the section position, MDCT perfusion images were obtained by administering 81.65 g iomeprol equivalent to 40 g iodine with a 100 ml 4 ml/sec flow rate through the antecubital vein using an automatic injector (Ulrich Medical, Chesterfield, MO, USA). The patients were told to hold their breath or to breath superficially during the acquisition. Acquisition time was 40 to 60 seconds. The arterial structure in the section where the mass was located was used as the input artery in the deconvolution analysis method in each patient. The arterial structures used were the ascending and descending aorta.

Image Analysis

After transferring the images obtained to the Vitrea workstation, their colored perfusion maps were prepared. Parameters measurements were performed by placing the ROI in 3 different locations in the solid sections while avoiding the necrotic cystic areas of the masses as much as possible. The obtained BV, BF, TTP, MTT perfusion parameters were recorded (Figure 1).

Statistical Analysis

Statistical evaluation of our research data was performed with the SPSS for Windows, version 13.0, statistical software program (SPSS Inc., Chicago, IL, USA). Data regarding all measurable variables were presented as arithmetic average (X) ± Standard Deviation (SD). The Shapiro-Wilks normality test was used to test whether measurable variables showed normal distribution. Some of the variables were found to show normal distribution ($p > 0.05$), and some not to show normal distribution ($p < 0.05$). The unpaired *t* test, Kruskal-Wallis variance analysis

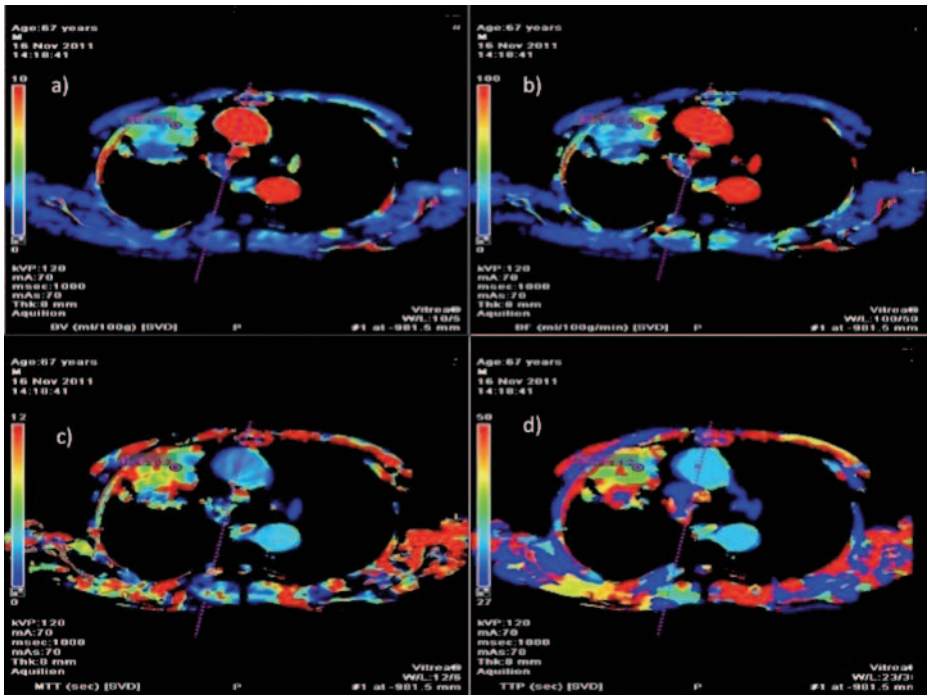

Figure 1. Colored perfusion map and ROI measurements of the peripheral mass (histopathological diagnosis: adenocarcinoma). ***A,*** BV value of the mass was measured as 10.2±0.8 ml/100 g. ***B,*** BF value of the mass was measured as 58.6±8.3 ml/100 g/min. ***C,*** MTT value of the mass was measured as 10.6±1.7 sec. ***D,*** TTP value of the mass was measured as 31.7±9.1 sec.

Table I. Comparison of BF, BV, TTP and MTT values of the masses according to their SCLC and NSCLC diagnoses.

	n	BV	BF	MTT	TTP
SCLC	13	5.87 ± 4.09	35.32 ± 19.32	10.17 ± 3.84	36.92 ± 13.53
NSCLC	31	6.83 ± 2.89	37,95 ± 16.9	11.23 ± 3.37	36.50 ± 11.47
p		0.217	0.529	0.487	0.917

and Mann-Whitney U test were used to compare our variables in terms of diagnosis, localization, necrosis and solidity. $p < 0.05$ was accepted as statistically significant.

Results

The cases were primarily classified as SCLC and NSCLC according to their cytological/histopathological diagnoses. The number of cases diagnosed with SCLC was 13; the number of cases diagnosed with NSCLC was 31. Of 31 patients with NSCLC, 11 were adenocarcinoma, 13 were squamous cell carcinoma and 1 had large cell carcinoma. The histopathological sub-typing of the remaining 6 patients with NSCLC could not be performed. Solid and necrotic SCLC and NSCLC cases were evaluated in two groups. 13 patients had a mass with necrotic characteristics and 31 patients had a solid mass. Lung masses observed on thorax CT were evaluated after classifying them as central or peripheral. There were 10 patients with a peripheral lung mass and 34 with a central mass.

The TTP values of SCLC and NSCLC cases showed a normal distribution and no statistically significant difference was found when compared. BV, BF, and MTT values of SCLC and NSCLC cases did not show a normal distribution and no statistically significant difference was found when compared (Table I).

No statistically significant difference was found when the BV, BF, MTT and TTP values of patients with a histopathological diagnosis of adenocarcinoma, squamous cell carcinoma and SCLC were compared (Table II).

The BF values of central and peripheral lung cancers showed normal distribution and a statistically significant difference was found when they were compared. No statistically significant difference was found for TTP values. The BV and MTT values of central and peripheral lung cancers showed a normal distribution and a statistically significant difference was found when compared (Table III).

TTP values of solid and necrotic lung cancers showed a normal distribution and no statistically significant difference was found when compared. A statistically significant difference was found when MTT values were compared (Table IV). The BV and BF values for solid and necrotic lung cancers did not show a normal distribution and statistically significant difference was found when compared (Table IV).

Table II. Comparison of the masses according to their histological diagnoses and BF, BV, TTP and MTT average values.

	n	BV	BF	MTT	TTP
Adenocarcinoma	11	6.99 ± 2.81	39.12 ± 16.98	11.63 ± 3.19	38.69 ± 9.69
Squamous Cell Carcinoma	13	7.33 ± 3.4	31.77 ± 19.19	10.81 ± 3.54	31.77 ± 8.81
SCLC	13	5.67 ± 4.00	35.36 ± 18.56	9.91 ± 3.81	35.25 ± 14.42
p		0.367	0.878	0.695	0.185

Table III. Comparison of central and peripheral masses according to their BF, BV, TTP and MTT average values.

	n	BV	BF	MTT	TTP
Central	34	5.65 ± 2.96	30.45 ± 11.25	10.13 ± 3.01	35.71 ± 13.32
Peripheral	10	9.62 ± 2.34	60.05 ± 15.49	13.56 ± 3.91	39.71 ± 4.36
p		0.0001	0.0001	0.028	0.359

Table IV. Comparison of solid and necrotic masses according to their BF, BV, TTP and MTT average values.

	n	BV	BF	MTT	TTP
Necrotic	13	5.40 ± 2.32	29.23 ± 11.72	10.04 ± 1.55	39.28 ± 8.75
Solid	31	7.03 ± 3.51	40.51 ± 18.52	11.28 ± 4.02	35.50 ± 13.03
p		0.006	0.049	0.289	0.346

Discussion

Lung cancers rank first among cancer-related deaths. They are responsible for 31% and 25% of cancer-related deaths in males and females respectively. The lung cancer related mortality rate is higher than the total of the mortality rates related to colon, breast, and prostate cancers[3]. In general, lung cancers are analyzed in two groups as SCLC and NSCLC. SCLC cases make up approximately 16-20% of all lung cancers. SCLC cases show a rapid spread from the beginning, are considered widespread disease and are sensitive to chemotherapy[4,5].

NSCLC cases make up approximately 80% of lung cancers. Many patients with NSCLC have advanced stage disease at diagnosis and the prognosis continues to be very poor in these cases. Metastases occur in course of the disease of more than half of the patients suitable for curative resection[6].

The most important factors in planning treatment and determining the prognosis in lung cancer are cell type and staging. Survival is related to the stage of the lung cancer and how early the tumor is diagnosed[7].

TNM staging has an important role in the determination of surgical option, treatment protocol and prognosis in patients with lung cancer. Thorax CT is important in this staging[8].

Despite all the new treatment models, control of advanced stage disease is extremely difficult in both lung cancer types. Studies on the molecular biology of lung cancer have accelerated in recent years leading to accumulation of important knowledge[9].

Angiogenesis is necessary for tumor growth and is one of the significant events in the neoplastic process[10]. Vascular endothelial growth factor is the most important and most emphasized angiogenic molecule[11]. Most tumors are neovascular when they are diagnosed[12]. There is experimental and clinical evidence indicating that angiogenesis facilitates both local spread and distant metastasis of the tumor[13]. A tumor cell needs to enter the vascular system, remain alive in the circulation, stop at the microveins of the target organ, exit the vascular system, grow in the target organ and overcome various barriers to stimulate angiogenesis in order to carry out metastasis microveins, exit vascular system, grow in the target organ and overcome barriers such as stimulate angiogenesis in order to carry out metastasis[14,15]. Clinical indicators show that metastasis characteristics of the tumor depend on the extent of the angiogenesis[16].

The importance of tumor angiogenesis in tumor staging has attracted the attention of the radiological community. Increase in MVD causes tumor perfusion *in vivo* and an increase in blood volume in the tumor as indicated by the BV parameter[17,18].

CT is still the primary imaging method in oncology. Malignant and benign lesion differentiation is difficult in many patients with a solitary pulmonary nodule in the lung. Swenson et al[19,20] found a correlation between PEI in CT and the histopathologic MVD values of the masses in benign and malignant SPNs. They found 98% sensitivity and 58% specifity values in malignant and benign SPN differentiation in another classification with increased number of the patients.

Zhang et al[21] evaluated blood flow in SPNs with dynamic CT study and obtained similar results.

Miles et al[22] found higher perfusion parameters and a serious correlation between these values and FDG uptake in advanced stage lung cancers.

Li et al[23] studied PEI, TTP and BV values in their first perfusion CT study on total of 77 patients with solitary pulmonary nodules of whom 46 were malignant, 22 benign and 9 active inflammatory non-calcified. The PEI and BV values in benign SPNs were found to be lower than in malignant and active inflammatory SPNs. This study emphasized that the differentiation of benign and malign lesions could be made using perfusion studies performed with MDCT. Perfusion parameters were evaluated with MDCT in another study on 97 patients with histopathologically proven peripheral lung carcinoma with a size of 5 cm at most. No statistically significant difference was found between lesion histopathological types and the PEI, TTP and BV parameters in the study.

However, perfusion values of peripheral lung carcinomas with distant metastasis were higher than lesions without metastasis. The study concluded that perfusion evaluation with the 64-detector CT was a valuable method in the evaluation of peripheral lung cancers and it was possible that it was associated with tumor size and metastatic lesion perfusion parameters in lung cancer[24].

BF values measured from the lesions diagnosed as squamous cell carcinoma were found to be higher than the lesions diagnosed with adenocarcinoma in a study performed in 24 patients with NSCLC, and perfusion CT was emphasized to be a useful method in NSCLCs at the end of the study[25].

We found no statistically significant difference between the perfusion parameters according to the histopathological types of the patients with lung cancer.

Ng et al[26] measured tumor permeability and BV values in tumor masses of 10 mm and 40 mm along the z axis with 16-detector CT in 10 patients with histopathologically confirmed NSCLC in a study they conducted and examined the change and repeatability in the perfusion values in both groups. The results obtained from the of 40 mm tumor section in the z-axis were observed to be more accurate and to provide much clearer results in terms of reproducibility of the analysis at the end of the study. We performed our study using a region of 32 mm along the z axis of the tumors in our study.

Kiesling et al[27] investigated the perfusion and PEI values with MDCT in their study on 24 patients with bronchial lung carcinoma and they found the mean perfusion values lower with larger tumor volume when they classified these values according to the size, localization and histopathological types of the lesions. They also found the perfusion values of the centrally located lesions to be lower than the peripheral lesions. However, no significant difference was found between the PEI values of peripheral and centrally located lesions. No statistical significant difference was found between the patients with SCLC and NSCL in terms of perfusion parameters.

We also found no statistically significant difference regarding the perfusion parameters according to the histopathological type of the lung cancers in our study. Perfusion values were statistically significantly higher in peripheral lung masses than central masses in our study.

A strong washout was observed in cavitary lesions caused by malignancy in a perfusion CT study with 53 masses with cavitary lesions. CT obtained from the cavitary lesions was suggested to be insufficient by itself and the use of perfusion CT in addition to thorax CT was recommended for the differential diagnosis of cavitary lesions[28].

We made measurements by placing ROI in 3 different regions of solid sections that were not necrotic in masses with a necrotic cavity in our study, avoiding the regions of necrosis as much as possible.

Fraioli et al[29] evaluated the perfusion CT parameters before chemotherapy and anti-angiogenic treatment and 40^{t} and 90 days later in 45 patients with a histopathologically proven unresectable adenocarcinoma in their study and found the BF, BV and PS values of tumors that respond to treatment to be higher. Perfusion CT is emphasized as an alternative method in the evaluation of cancer angiogenesis and is reported to be effective in guiding the treatment.

Despite several studies suggesting that perfusion CT can be used effectively for cancer angiogenesis, doubts exist regarding the quantitative values of perfusion parameters measured from tumors. Goh et al[30] analyzed the BV and permeability values in 44 patients with colorectal cancer with two different methods. They found different results from the methods for tumor vascularity and emphasized that it was not possible to use different methods interchangeably for perfusion CT applications.

Higher perfusion parameter values in high-grade and metastasizing tumors in perfusion CT and higher sensitivity to radiotherapy and chemotherapy of tumors with high perfusion values in the literature suggest that MVD and tumor neovascularization are higher in peripheral and solid lung masses.

Conclusions

First-pass perfusion CT is a rapid, and easy applicable method for lung cancers. The non-invasive evaluation of tumor perfusion by first-pass perfusion CT in lung cancers provides valuable information about tumor angiogenesis. However, we believe that peripheral and solid lung cancers will benefit more from treatments such as anti-angiogenetic drugs, radiotherapy and chemotherapy than central and necrotic lung cancers and that perfusion CT will play a greater role in the evaluation of the efficiency of these treatments in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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