The Role of First-Pass Perfusion Computed Tomography in the Differentiation of Centrally Located Lung Cancer and Distal Atelectasis

Mehmet Fatih Erbay[1]; Tamer Baysal[2], Zeynep Ayfer Aytemur[3]

[1] Hospital of Gözde Akademi, Department of Radiology, 44100, Malatya, Turkey

[2] Dr. Lutfi Kirdar Education and Research Hospital, Department of Radiology, 34100, Kartal, İstanbul, Turkey

[3] Department of Pulmonary diseases, Faculty of Medicine, Inonu University, 44280 Malatya, Turkey

Abstract

Our aim in this study was to differentiate postobstructive consolidation from lung cancer by means of first-pass perfusion CT in centrally located malignancies. We studied 20 patients (18 males and 2 females) diagnosed as lung cancer with untreated central masses and distal postobstructive atelectasis. In order to localize the slice position showing the appropriate mass-consolidation area to be included in contrast-enhanced dynamic imaging, we first performed scout and baseline acquisition without contrast media, followed by dynamic acquisition after intravenous contrast media injection. Three different ROIs were placed on the central mass while avoiding the peripheral regions as much as possible and on the peripheral locations of distal consolidation using dynamic contrast-enhanced images. The BV, BF, TTP and MTT perfusion parameters were automatically calculated in the ROI locations. We were able to differentiate the central masses from distal consolidations by means of statistical differences in the first-pass BV and BF parameters between the mass and distal consolidation areas. The mean values of parameters that were calculated in the mass and consolidation areas were BV:7.69±4.28 ml/100g, BF:48.87±25.54 ml/100g/min, TTP:27.94±7.32 sec., MTT:9.56±3.47 sec. and BV:11.83±5.34 ml/100g, BF:78.75±39.41 ml/100g/min, TTP:29.72±6.05 sec., MTT:11.44±4.93 sec., respectively. We concluded that first-pass perfusion CT may be used as a functional imaging method to differentiate central lung cancer from distal consolidation and could be useful in reducing the target cancer volume in patients who are candidates for radiation therapy.

Keywords: Perfusion Computed Tomography (CT), first-pass, postobstructive consolidation, central lung carcinoma

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Corresponding Author: Hospital of Gözde Akademi, Department of Radiology, 44100, Malatya, Turkey
E-mail: drfatiherbay@hotmail.com **Phone**: +90532 335 69 38

Introduction

The use of non-invasive functional imaging methods in the detection, staging and follow-up of lung cancer has gradually become routine in clinical applications [1]**.** Perfusion CT is one of these methods and is a promising technique that allows functional evaluation of tissue vascularity [2]. Perfusion CT has a wide spectrum of clinical and research applications and is also being used increasingly more commonly in oncology. Its clinical applications in oncology include lesion characterization for the differentiation of benign and malignant lesions, screening for occult malignancy, prognosis prediction based on tumor vascularity, and the evaluation of the therapeutic effectiveness of many treatment methods [3,4].

Lunc cancer is the most common causes of cancer deaths [5,6]. The differentiation of a centrally located tumoral mass from collapsed lung segments is especially important as current radiotherapy aims to target the tumoral tissue better, thus decreasing the dose of unnecessary radiation that normal tissues are exposed to [7]. Current radiotherapy applications use computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) for this purpose. One of the important issues in radiotherapy is differentiation of the tumor tissue from the distal consolidation areas. This differentiation is not always possible with conventional methods.

Our aim in this study was to differentiate the central mass from postobstructive atelectasis consolidation in centrally-located lung cancers with atelectasis consolidation using first-pass computed tomography perfusion parameters. Such differentiation will enable the exposure of the mass to the planned dose of radiation while the consolidation area is protected.

Material and Method

Cases

This study was conducted at Inonu University's Radiology Department on a total of 23 patients (21 males and 2 females) diagnosed with lung cancer following cytology and histopathology evaluations between June 2009 and November 2010. The mean age was 64.3 (45-79) years. We included patients who had not received radiotherapy with a centrally-located lung tumor and a consolidation area consistent with atelectasis or postobstructive

pneumonia distal to it in the study. Three patients with acquisitions that did not conform with the imaging protocol, or with an artifact due to patient motion were excluded.

Our study was approved by the Inonu University Faculty of Medicine Ethics Committee with decision number 2009/53 dated May 26, 2009 and informed consent was obtained from the subjects.

Imaging and Analysis

A 64-detector multislice computed tomography device (Aquilion 64 Model TSX-101A; Toshiba Medical Systems, Corporations Tochigi Japan), was used to first obtain scout and standard non-contrast images for every patient, followed by dynamic imaging and the determination of the slice position that included the mass and consolidation areas. Once the slice position was defined, an automatic syringe (Missouri, Ulrich Medikal, 31 The Netherlands) was used to inject 81.65 g iomeprol (İomeron 400, Braccos.p.a. Milano, Italy) with an equivalent of 40 g iodine in 100 ml from the right antecubital vein at a flow rate of 5 mL/s intravenously to obtain multislice CT perfusion images. The patients were asked to hold their breath or breathe slowly during the procedure. The acquisition duration varied between 40 and 60 seconds. Deconvolution analysis was used to place a ROI on the ascending aorta as the input artery in every case and color perfusion maps were prepared. The descending aorta was selected as the input artery when the ascending aorta was not within the section. Contrast dynamic CT images of the patient were used to place ROI in 3 different localizations while avoiding the periphery of the central mass as much as possible. We also placed ROI at 3 different localizations in the periphery of the distal atelectasis area. The acquired images were transferred to a workstation for analysis and then evaluated with the Vitrea perfusion software. ROI were placed at 3 different localizations in the mass and distal atelectasis areas using the color perfusion maps. The values of the BV, BF, TTP and MTT parameters were recorded.

Statistical Analysis

The SPSS for Windows version 13.0 statistical software was used for the statistical analysis of our study. Quantitative data were provided as mean (x) ± standard deviation (SD). Our qualitative data were tested with the Shapiro-Wilks normality test. We used the unpaired t-test

to evaluate the quantitative data with a normal distribution, and the Mann-Whitney U test to evaluate the quantitative data without a normal distribution. $p<0.05$ was considered statistically significant.

Results

BV:7.69±4.28 ml/100g, BF:48.87±25.54 ml/100g/min, TTP:27.94±7.32 sec., MTT:9.56±3.47 sec. and BV:11.83±5.34 ml/100g, BF:78.75±39.41 ml/100g/min, TTP:29.72±6.05 sec., MTT:11.44±4.93 sec., respectively.

The cases were grouped according to their histopathology diagnoses. The tumors were grouped as small cell (SCLC) and non-small cell lung cancer (NSCLC) according to their cytology/histopathology diagnoses. There were 7 SCLC and 13 NSCLC cases.

Comparison of the mean TTP (27.94 ± 7.32 sec., 29.72 ± 6.05 sec. respectively) and MTT (9.56 ± 3.47 sec., 11.44 ± 4.93 sec. respectively) values for the masses and consolidation areas that did not show normal distribution revealed no statistically significant difference (Figure 1).

Comparison of the mean BV (7.69 ± 4.28 ml/100g, 11.83 ± 5.34 ml/100g respectively) and BF (48.87 ± 25.54 ml/100g/min , 78.75 ± 39.41 ml/100g/min respectively) values for the masses and consolidation areas that showed normal distribution revealed a statistically significant difference (Figure 2).

Comparison of the mean BF, BV, TTP and MTT values by histology diagnoses of the masses showed no statistically significant difference (Table 1) (Figure 3).

Comparison of the mean BF, BV, TTP and MTT values by histology diagnoses of the masses again showed no statistically significant difference (Table 2) (Figure 4).

The consolidation (Figure 5) and central mass (Figure 6) color perfusion maps and ROI measurements of one case (K.A.) are presented below.

Table 1. Mean BF, BV, TTP and MTT values of the masses according to the histological diagnoses

	n	*bfo*	*Bvo*	*ttpo*	*mtto*
SCLC	7	52.20±27.24	9.21±6.39	27.91±4.84	8.77±4.31
NSCLS	13	47.07±25.53	6.87±2.56	27.95±8.56	9.98±3.04

SCLC: small cell lung cancer
NSCLC: non-small cell lung cancer

Table 2. Mean BF, BV, TTP and MTT values of the consolidation areas according to the histological diagnoses of the masses

	n	*bfo*	*bvo*	*ttpo*	*mtto*
SCLC	7	82.22±24.54	10.45±5.66	30.80±5.39	11.11±2.77
NSCLC	13	76.87±46.34	12.58±5.24	29.14±6.51	11.62±5.88

SCLC: small cell lung cancer
NSCLC: non-small cell lung cancer

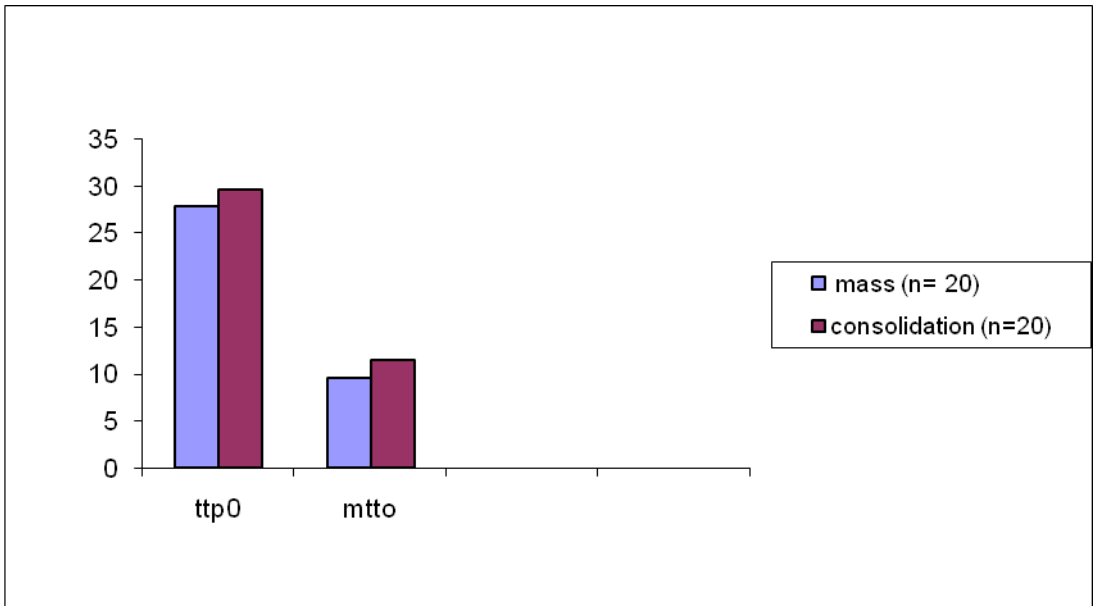


Figure 1. Comparison of the TTPo and MTTo parameters of the mass and consolidation areas

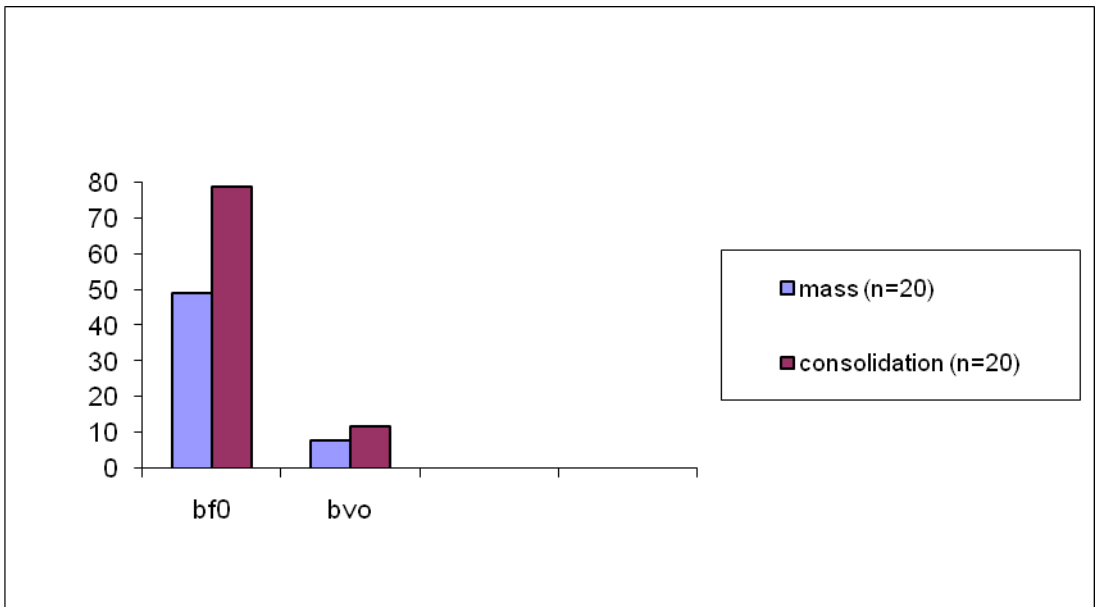


Figure 2. Comparison of the BFo and BVo parameters of the mass and consolidation areas

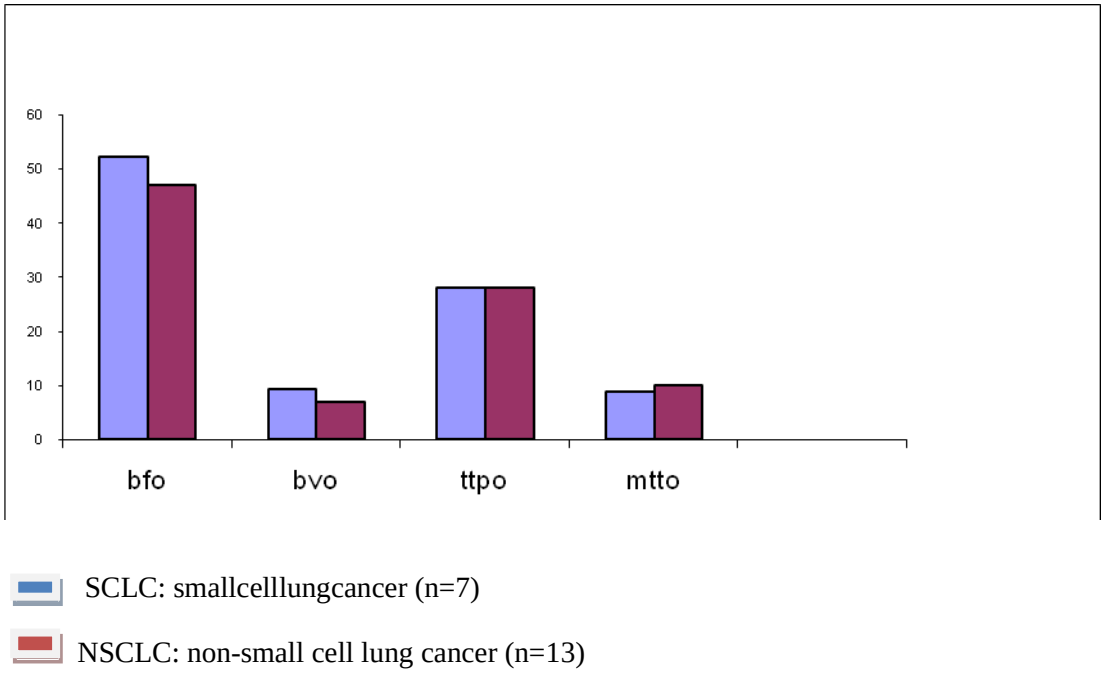


Figure 3. Comparison of the masses according to histological diagnoses

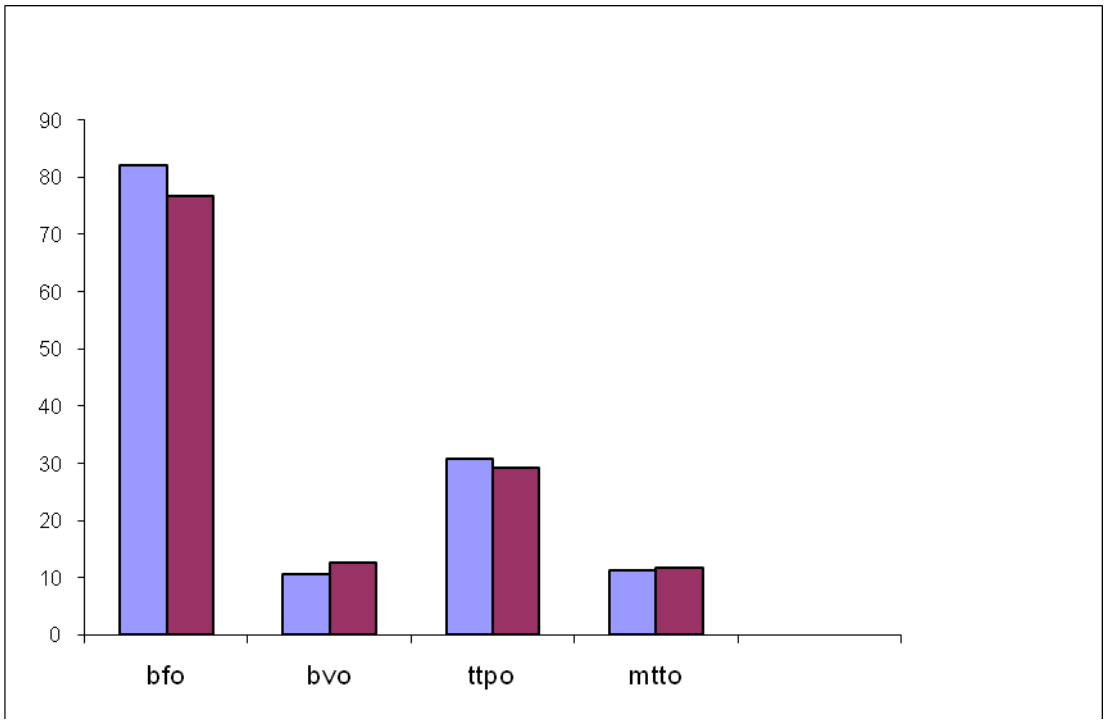
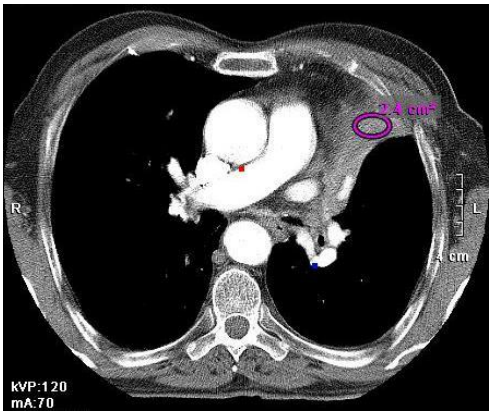
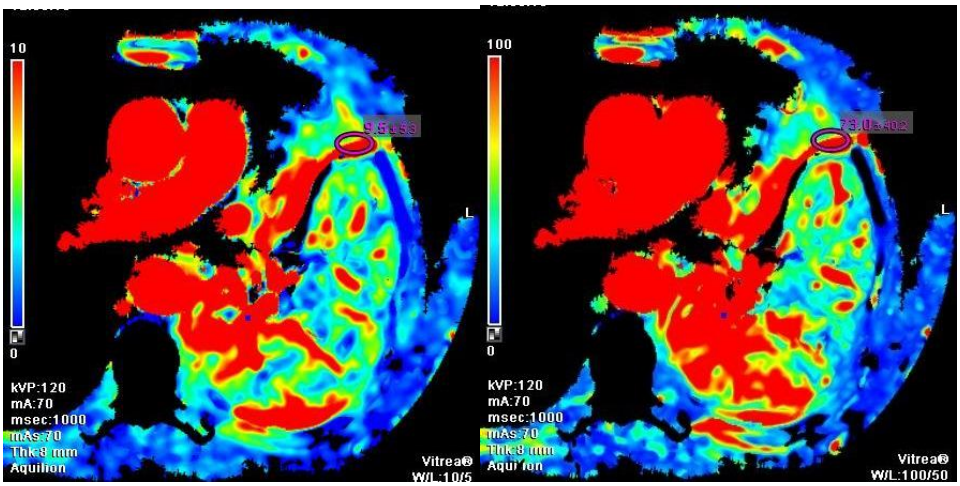


Figure 4. Comparison of the consolidation areas according to the histological diagnosis of the mass

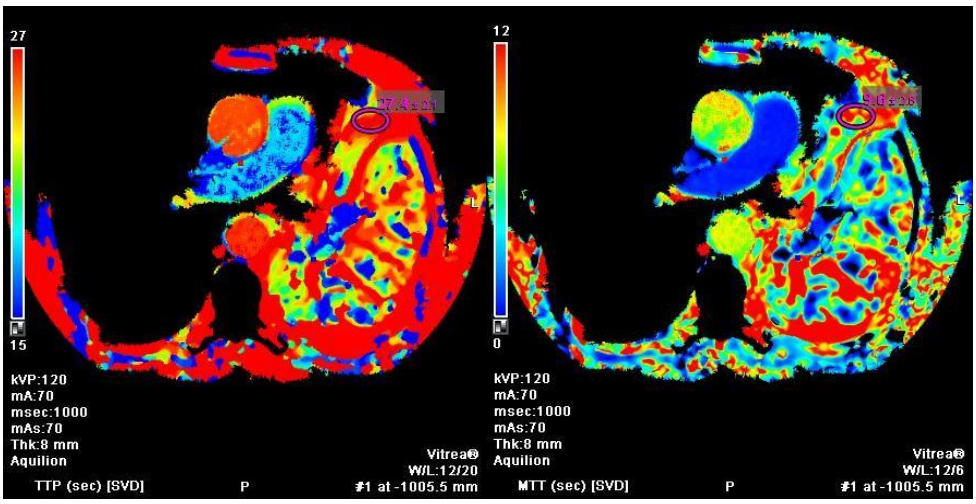
Figure 5. Perfusion maps of the consolidation areas



a)



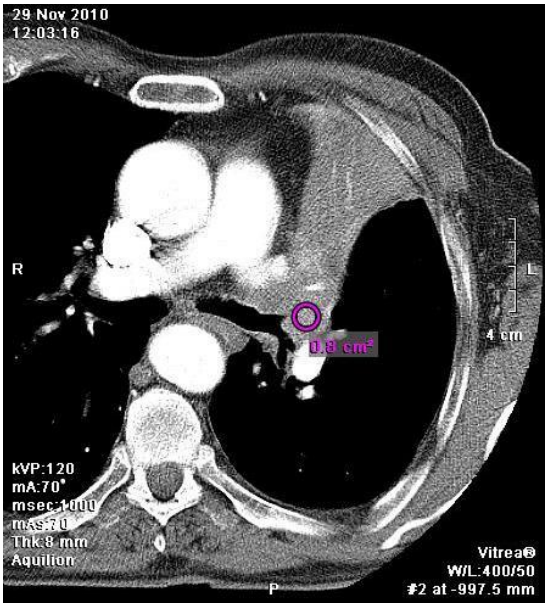
b) c)



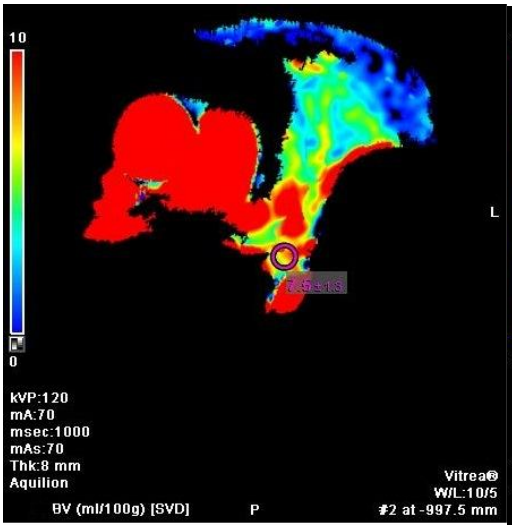
d) e)

a) Consolidationarea on where ROI wasreplaced, in thecontrastenhancedaxialthorax CT slice
b) BV value of consolidationarea has beenmeasured as 9.5±5.3 ml/100g
c) BF value of consolidationarea has beenmeasured as 73±40.2 ml/100g/min
d) TTP value of consolidationarea has beenmeasured as 27.4±2.1 sec.
e) MTT value of consolidationarea has beenmeasured as 9.6±2.6 sec.
(Pathologicaldiagnosis: smallcelllungcancer)

Figure 6. Perfusion maps of the masses



a)



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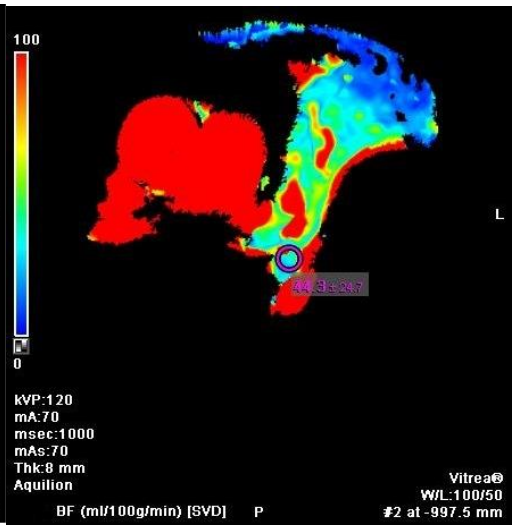
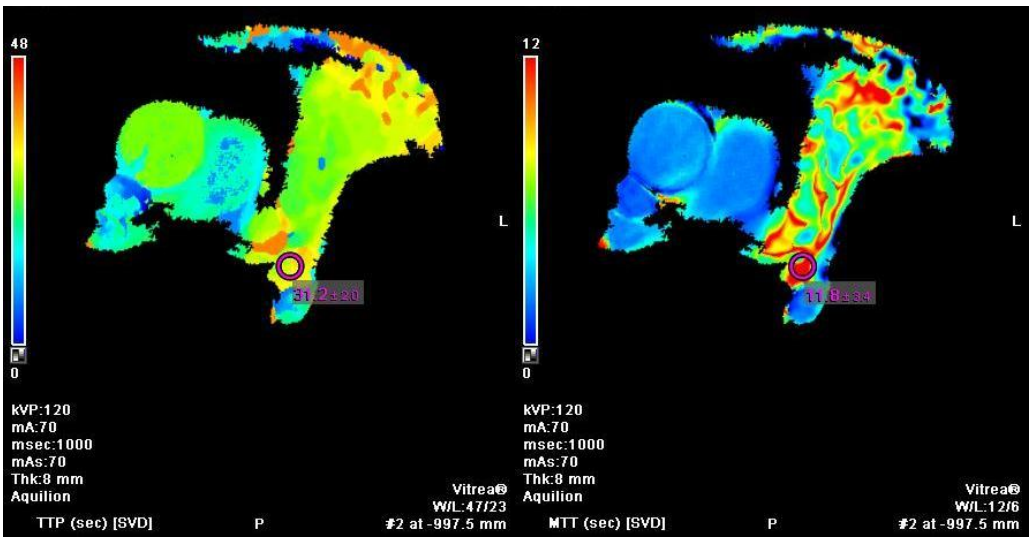


c)



d) e)

a) Central massarea on where ROI wasreplaced, in thecontrastenhancedaxialthorax CT slice
b) BV value of themass has beenmeasured as 7.5±1.3 ml/100g.
c) BF value of themass has beenmeasured as 44.3±24.7 ml/100g/min.
d) TTP value of themass has beenmeasured as 31.2±2.0 sec.
e) MTT value of themass has beenmeasured as 11.8±3.4 sec.

Discussion

Lung cancer is the most common cause of cancer deaths worldwide [5]. Lung cancers can be classified as central and peripheral according to their anatomical localization. Centrally-located tumors usually cause volume loss at the distal part of the bronchus or bronchiole that they obstruct [8]. The postobstructive consolidation or pneumonia can lead to a volume loss pattern that is segmental or lobar or includes the whole lung. It can be difficult to differentiate tumor tissue from peripheral consolidation areas due to the distal atelectasis and secretion retention caused by central tumor obstruction and the secondary pneumonia. Volume loss can be better evaluated with CT in many cases when the area of volume loss has necrotic areas within the large exophytic component of the central lesion [9,10]. The proximal sections of the segmental bronchi and the lobar bronchi can be shown with very high quality in normal individuals. CT is a reliable modality with an acceptable false positive value in defining an obstructive tumor as the cause of atelectasis [10].

It is important to differentiate a centrally-located tumor from a collapsed lung segment as current radiotherapy administration, one of the treatment options for nonresectable disease, aims to better target tumoral tissue and therefore decrease unnecessary radiation exposure of surrounding normal tissues [7,11].

There are some studies in the literature aiming to differentiate between a central mass and the accompanying atelectasis tissue. A study on MR and CT imaging in the differentiation of proximal bronchogenic carcinoma from postobstructive lobar collapse has compared the definition and mass-collapsed segment differentiation using CT attenuation levels and MR signal changes based on the central tumor contour abnormalities. No difference was found between the attenuation levels of distal lobar collapse and the proximal tumor in pre-contrast images. Contrast dynamic CT imaging revealed that the collapsed segment showed more contrast enhancement than the tumor in 8 of the 19 patients and these two tissues had different attenuation levels. The same study was also able to differentiate between tumor and collapsed segment by usıng the MRI signal intensity differences [12]**.** Another study with the rapid CT acquisition technique has reported that there was marked contrast enhance of the collapsed segment between 40 sec and 2 min while the proximal tumor showed slow and minimal enhancement when a bolus contrast injection was performed [13]**.** The role of conventional MRI in differentiating the central tumor from postobstructive atelectasis is still controversial [12]. There are studies claiming that the in vivo T1 and T2 signal intensity of malignant tumors significantly overlaps the values of benign processes in the lung parenchyma [14,15].

A few studies have tried to differentiate postobstructive consolidation from central lung cancer with the DAG method. A DAG study has revealed that the ADC values of central carcinomas and postobstructive consolidation have a statistically significant difference with the ADC values of consolidation higher than that of the mass. The study also calculated the ADC values of pneumonic consolidation and atelectasis developing due to benign pathologies and did not find a statistically significant difference between these values and the ADC values of consolidation developing secondary to central carcinomas. There was also no significant difference between the mean ADC values of central and peripheral carcinomas and consolidation areas developing due to various types of carcinomas. They also did not find any statistically significant difference between the mean ADC values of carcinomas of various histopathological types [7]. A similar study used DAG to detect tumor in collapsed lung

tissue. The densities and signals of the tumor tissue and the postobstructive collapsed lung tissue were compared with contrast CT, T2A and DAG. It was possible to differentiate cancer and postobstructive collapsed lung with DAG in 26 of 33 patients. Differentiation was possible in 88% of the cases using a combination of DAG and T2A images and it was suggested that DAG can be used to differentiate lung cancer from collapsed lung tissue [16]**.** Susceptibility and motion artifacts were emphasized as the main limiting factors of DAG in both studies [7,16].

A retrospective study has reported that it was possible to limit the radiotherapy area with the FDG-PET method in 10 of 34 postobstructive atelectasis patients. The data supporting PET replacing conventional methods instead of its current adjunct role in detecting extrathoracic metastases are inadequate [17]**.** It is not currently possible to use the PET system routinely as it is new and expensive.

Perfusion CT application is a promising CT technology that enables functional determination of tissue vascularity. Contrast substance is administered with a bolus injection and the gradual changes in tissue density are measured with dynamic CT series in this method[2]**.** Perfusion CT provides a larger spectrum for clinical and research applications thanks to the rapid technological advances in MDCT systems and the use of commercial software. Perfusion CT is also being used increasingly more commonly for oncology applications. Clinical applications in oncology include lesion characterization for benign-malignant differentiation, definition of occult malignancies, prognostic prediction based on tumor vascularity and the evaluation of the therapeutic effectiveness of various treatment methods [3,18]. The development of new antiangiogenic drugs requires functional imaging methods such as perfusion CT or dynamic contrast MRI to evaluate their therapeutic effectiveness [19,20,21]. Taking into account that functional changes appear before morphological changes during treatment, methods such as perfusion CT enable earlier evaluation of the treatment's effectiveness compared to conventional methods [20].

There are only a few studies evaluating the differentiation of proximal bronchogenic carcinoma from postobstructive collapse. Onitsuka et al. have shown the difference between the contrast patterns of the central tumor and the distal collapsed segment and have

emphasized that this difference reaches its maximum level between 40 and 120 seconds during the imaging process [3].

Although there are many previous studies using the perfusion CT method to investigate various aspects of lung cancers [1,22,23], there are no perfusion CT studies on the differentiation of central tumor and postobstructive atelectasis. Comparison of the first-pass perfusion parameters in our study revealed that the mean BV and VF values from the central mass were statistically significantly lower than the values from atelectasis areas. However, the fact that these parameters that reflect the blood flow rate and blood volume within the tissue are higher in the atelectasis area indicates an increase in blood flow within a unit volume, possibly due to the supply of the collapsed segment from the larger pulmonary artery branches while the tumoral tissue is supplied from the relatively narrower bronchial arteries [13].

A CT perfusion study in lung cancers has revealed lower perfusion in centrally-located masses than peripheral ones [1]. This perfusion difference has been explained by the lower vascular density in the central lung tissue and the obstruction of the vessels by the tumor. It has also been claimed that a different growth pattern is present in central and peripheral tumors, independent of tumor histology. We found lower perfusion values than those reported in the literature for central masses. We were unable to compare the CT perfusion values of central and peripheral masses as we did not include peripheral lung cancers in our study. Li et al. have studied total tumor perfusion in peripheral lung cancers with a 64-detector CT and shown that the perfusion values of tumors with distant metastases were statistically significantly higher than those without distant metastases. The perfusion values decreased as the tumor size increased [22]. We did not find a statistically significant relationship between central tumor size and CT perfusion values in our study.

Ovali et al. have demonstrated that the BF values of squamous cell carcinoma cases are statistically significantly higher than adenocarcinoma cases in their study on 24 NSCLC cases using a thoracic perfusion CT technique. They emphasize that perfusion CT could be a useful method for NSCLC evaluation [24]. Kiessling et al. have studied perfusion CT findings in advanced stage bronchial carcinoma patients and found no difference in the perfusion (or BF) and PE (peak enhancement) parameters between SCLC and NSCLC cases [1]. We also did

not find a statistically significant difference between the SCLC and NSCLC groups we had created according to the histopathology diagnosis in centrally-located tumors.

There were also some factors with a negative influence on CT perfusion in our study. Perfusion values can be measured incorrectly in tumor areas close to large central vessels due to a beam hardening artifact. These artifacts can be controlled by using higher tube voltages. This approach requires careful evaluation of the patient's radiation exposure.

We only evaluated the early stage pass of the contrast matter in this study. A longer protocol will enable evaluation not only of tissue perfusion but also of capillary permeability, blood flow and tumor blood volume. However, such an approach will also prolong the procedure and create a disadvantage regarding routine use in the clinic.

In conclusion, we believe that it is possible to differentiate central lung cancers from distal postobstructive atelectasis using first-pass perfusion CT parameters. This differentiation will help ensure a narrower safety range and decrease radiation toxicity in the normal tissue surrounding the tumor in patients about to receive radiotherapy during clinical procedures.

Conflicts of Interest

The authors declared no conflicts of interest.

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