Effectiveness of Twin-Beam Dual-Energy Computed Tomography in Characterization of Solitary Pulmonary Nodules

Abstract

Objective: The aim of this study is to investigate the effectiveness of Dual-Energy Computed Tomography including visual assessment, iodine concentration, and contrast load for the discrimination between benign and malignant pulmonary nodules.

Materials and Methods: The images of the patients with 53 pulmonary nodules that were taken with dual energy thoracic computed tomography, 40 seconds after intravenous contrast administration, were obtained with a single-source dual-energy computed tomography (120kV Split Filter) with twin beam technology, and a dual-energy was done at work station (SyngoVia; Siemens Medical Solutions). Color map evaluation findings in visual enhancement, contrast and iodine loads were calculated and noted separately for each of the 53 solitary lung nodules.

Results: A total of 53 patients 26 (49%) male and 27 (51%) female) with a solitary pulmonary nodule fulfilled the inclusion criteria. Among 53 pulmonary nodules, 17 (32.1%) were malignant and 36 (67.9%) were benign. Of the benign lesions; 18 were detected in males (30.7%) and 18 in females (33.3%).

There was not a statistically significant difference in age between two groups (p=0.284).

The mean contrast load of the malignant nodules is significantly higher than that of benign nodules (p=0.034). The mean iodine load of the malignant nodules is significantly higher than that of benign nodules (p=0.031). The frequency of red/orange appearance was significantly higher in malignant nodules than benign ones (p:0.006).

Conclusion: We think that dual-energy computed tomography will make significant contributions to the differentiation of benign and malignant in solitary pulmonary nodular lesions detected in the lung, with three different approaches such as visual on the image on the iodine coating color map, iodine concentration and iodine contrast load quantitatively.

Keywords: Dual Energy, Benign, Malignant, Pulmonary Nodule, Twin-beam, Iodine map, Contrast load, Iodine load

INTRODUCTION

The solitary pulmonary nodules are common lesions on routine radiological evaluation of the thorax which may be an early manifestation of lung malignencies. But an accurate discrimation of benign malignant conditions is sometimes a challenge because of the low sensitivity rate of both 18Fflourodeoxyglucose (FDG) positron-emission tomography (PET) and CT-guided biopsy for the relatively smaller (< 5 mm in size) nodules (1-2).

Nodules larger than 5 mm should be followed up according to defined risk factors and nodule characteristics. Lung nodules that have exhibited a stable course for at least two years, are considered benign (3). Therefore, the characterization of parenchymal nodules and the differentiation between benign and malignant tumors are critical for early diagnosis and prompt treatment. Recent technological advancements provided Dual-Energy Computed Tomography (DECT) imaging as a new technique to be used in the differential diagnosis between benign and malignant lesions based on the degree of contrast enhancement. This imaging method not only allows the evaluation of nodules by the shape, size, margins, and nature but also enables the user to assess the lesions by the contrast load, iodine load, and the image of contrast enhancement via the use of the dual-source technique (4). Many studies examined the DECT findings on various pulmonary lesions and vascular conditions including; pulmonary thromboembolism, pulmoner hypertension while data for differentiation between malignant and benign pulmonary nodules on DECT is very limited.

In this study, we aimed to compare the parameters of DECT including visual assessment, iodine load, and contrast load for the discrimination between benign and malignant pulmonary nodules.

MATERIALS AND METHODS

Patient Selection

This prospective study was approved by a university ethics committee with a number of 08 at the date of 15.05.2018. The patients who underwent at least one contrast-enhanced thoracic DECT scan for a solitary pulmonary nodule have histopathological examination results (after a transthoracic/ transbronchial or excisional biopsy) or at least 2 years of follow up CT scans in a tertiary university hospital between 2017-2019 were included in this study. The The Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON) study calculated the likelihood of developing lung cancer within 2 years and reported a very low potential for progression to cancer when the nodules have stayed stable for 2 years (3).

The histopathological examination results and thoracic CT images of the patients were reviewed on the hospital database and radiology department records. Patients with a nodule smaller than 6 mm, or purely calcified nodules were not included in this study. Fully calcified nodules were excluded from the study because such nodules are very likely benign and cause to calculate incorrectly high iodine

quantities and contrast load. Also, the patients whose histopathological examination results or follow-up CT scans for at least two years duration were not available, were excluded from the study.
According to histopathological examination results or size changes on follow-up CT scans nodules were classified as benign and malignant.
Solid ones of solitary nodules were included, all solitary lesions without systemic disease and unknown metastasis were included in the study.
A total of 53 patients with solitary pulmonary nodules were included in the study. The relationship between benign and malignant in gender, age, contrast load, iodine load and color map was evaluated.

Twin-Beam Dual-Energy Computed Tomography

Today, it is possible to perform DECT by using two X-ray tubes or a single X-ray tube that can be operated at different tube currents. This technique allows performing "double-energy" scanning, providing the opportunity to re-evaluate the data at 80 kVp and 140 kVp (5).As the difference between the amplitudes of the currents in the two tubes becomes higher (for example, between the amplitudes of 80 kVp and 140 kVp), the differentiation between two substances with different densities can be performed better (5). This technical advantage of DECT provides further benefits such as reduced radiation exposure compared to dynamic imaging studies and the increased capacity to detect calcifications (6). A twin beam on DECT is a new technique in which two equal tin and gold parts forms a split filter which is located in front of the tube output. This filter splits 120kVp X-ray beam to low and high-energy spectrum which are detected by a single detector (7).
Recent CT techniques utilizing dual-source CT scanners have been developed; enabling to obtain virtual non-contrast images and contrast-enhanced images at a single scan through the use of substance differentiation of iodine following the intravenous administration of an iodine-containing contrast agent (8). Thus, Hounsfield units (HU) can be obtained on a non-virtual image and the iodine value in the lung nodule can be obtained from the same Region of Interest (ROI). This technique can neglect the image acquisition process required for a non-contrast baseline study and can also diminish measurement errors occurring due to the different positions of the ROI in the baseline non-contrast and contrast-enhanced CT images. In addition, DECT can provide a perfusion map showing the distribution of iodine contrast agents in the lung parenchyma (5). Also, it can be used for the evaluation of the perfusion status of lung parenchyma before surgical resection.

In conventional dynamic CT scans, data are obtained by subtracting a basic non-contrast image from contrast enhanced images. Unlike conventional dynamic CT scans; both non-contrast and iodine contrast-enhanced images are simultaneously obtained from a single scan by performing DECT (9).

Scanning Protocol

DECT scanning was performed according to a special dual-energy protocol. All thorax scans were obtained by using the split-filter dual-energy mode (Siemens SOMATOM Definition AS + 128, Forchheim, Germany). Tomographic examinations were performed using a 512x512 pixel matrix, 64x0.6mm-collimation, a split filter (120AuSn) positioned in front of a 120 kV x-ray beam, 270 milliamperes (mA), and the dual-energy twin-beam mode of the somatom definition scanner (Siemens Medical Solutions) at 0.7 pitch and 0.5 s rotation time. All scans were performed in the supine position in a craniocaudal direction, including the entire thorax. An intravenous iodine contrast agent (iohexol (Omnipaque 350mg/50 ml) was administered with a dose of 1.3-1.5ml/kg at a rate of 1.6 mL/s by an automatic injector. Simultaneous scanning was performed by using a split filter and 120kV tube voltage (120AuSn) to obtain images. The 120 kV-split filter (120AuSn) data set and the weighted average image data set were transferred to a workstation (SyngoVia; Siemens Medical Solutions). The weighted average image; which could be used for routine 120 kV clinical applications, was generated automatically from the combination of the 140-kV and 80-kV data. Virtual non-contrast (VNC) and iodinated contrast-enhanced images were acquired on the workstation by using a modified prototype of the Syngo Dual Energy (Siemens Medical Solutions); which was a VNC application mode. Images were constructed on a 3 mm-thick thickness axial dataset.

Image Analysis

Each nodule was evaluated by a radiologist with 14 years of experience in thorax imaging who was blind to the histopathological results or previous radiologic features of the patients, regarding three different parameters. As the first evaluation, a qualitative visual evaluation was performed; in which a VNC image of the iodine component in a translucent mode was shown as a background color overlay. Because the manufacturer determined the iodine retention value as higher than 50% in the presence of default color-coding, the presence of any color (orange or red) in the nodule was considered contrast enhancement, and a black color (no color-coding) was considered lack of contrast-enhancement. The results were recorded in a dual fashion as "present" (orange-red) or "absent" (black) (**Figure 1-2).** Consequently, at least three ROI was drawn manually depending of the diameter of the lesion. The average of these measurement was calculated. Using the computer software, this average ROI provided us the presence of iodine and change of the HU values within the nodule. The second parameter is the attenuation change in density expressed in HU and the third one was the iodine concentration expressed in mg/ml **(Figure 3 - 4 - 5 - 6 - 7).**

Statistical Analysis

The variables were presented as mean ± standard deviation. A Mann-Whitney U test was used to compare iodine and contrast loads between benign and malignant nodules. A Receiver operating characteristic (ROC) analysis was performed to define a cut-off value of iodine and contrast loads for the discrimination between malignant and benign lesions. A chi-square test was used to compare the colors (Orange-red /black) of benign and malignant lesions. A $p<0.05$ was considered statistically significant. For statistical analysis, A SPSS Windows version 21.0 package software (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

A total of 53 patients (26 (49%) male and 27 (51%) female) with a solitary pulmonary nodule fulfilled the inclusion criteria. Among 53 pulmonary nodules, 17 (32.1%) were malignant and 36 (67.9%) were benign. Of the benign lesions; 18 were detected in males (30.7%) and 18 in females (33.3%). Among 17 malignant lesions, 8 observed in males and 9 in females. The difference in between males and females was not significant (p:0.203). The mean age of the patients with benign nodules was 58±14 years (age range: 25-75 years) with malignant nodules was 62±12 years (age range: 37-75 years). There was not a statistically significant difference in age between two groups (p=0.284). The largest nodule has a maximum diameter of 48mm while the smallest one has 6mm.

Histopathological examinations revealed that 9 (%52.9) of the malignant nodules were primary lung tumors (7 adenocarcinomas and 2 squamous cell carcinomas) and the other 8 (%47,1) were metastatic lesions (2 originated from breast and 6 from colon cancers). Of the benign nodules; 20

did not exhibit dimension changes on follow-up. Among 16 lesions with benign histopathological results; 8 were infectious lesions, 4 were hamartomas, one was tuberculoma, and one was granuloma one was a hydatid cyst, one was a bronchogenic cyst.

The mean contrast load was 56±152.8 (0-773) HU in benign nodules and 174.3±237.8 (22.5-834.0) HU in malignant nodules. The mean contrast load of the malignant nodules is significantly higher than that of benign nodules (p=0.034). The sensitivity and specificity rates of a cut-off density value of 19.25 HU for the contrast load were 100% and 66.7%, respectively positive predictive value (PPV) 58% and negative predictive value (NPV) 96%.

The mean iodine load was 3.6±8.9 (0-49.9) mg/ml in benign nodules and 10.3±13 (1.4-51) mg/ml in malignant nodules. The mean iodine load of the malignant nodules is significantly higher than that of benign nodules (p=0.031). The sensitivity and specificity rates of a cut-off value of 1.35 mg/ml were 100% and 69.4%, respectively (PPV: 60% and NPV: 100%).

Among 17 malignant nodules, 5 (29.4%) were black and 12 (70.6%) were orange/red on color maps. Of 36 benign nodules, 25 (69.5%) were black/white and 11 (30.5%) were orange/red. The frequency of red/orange appearance was significantly higher in malignant nodules than benign ones (p:0.006).

DISCUSSION

Pulmonary nodules are common lesions in clinical practise which requires detailed radiological and clinical evaluation because sometimes a malignant process may be an underlying cause. Also accurate identification of the lesions prevents unnecessary invasive/surgical procedures and iatrogenic complications in especially benign pulmonary nodules.Various conventional computed tomography techniques were used for differentiation of benign and malignant pulmonary lesions. Currently new techniques including DECT modified for better evaluation of the lesions by measuring contrast amount and enhancement (10).

It is very difficult to accurately measure the density of each component when multiple tissues present in a lung lesion on a conventional thorax CT because the HU value in a tomographic voxel measure both the iodine concentration and the average densities of the underlying different tissue types. Therefore; depending on the mass density, the obtained values can be used for measuring densities of two different substances (such as iodine and bone, etc.) at an average energy level (4). Thanks to the DECT technique, it is possible to obtain an additional attenuation value, which generates a difference between the two energies (11). The twin-beam dual-energy (TBDE), on the other hand, allows performing high-contrast dynamic studies via filtering the X-ray beam before it reaches the patient. Thus, the simultaneous acquisition of high and low kV data becomes possible in a single spectral CT scanning procedure. We used this technique in our study to distinguish between benign and malignant potentials of lung nodules. Scientific papers are available reporting that the split-filter dual-energy technique uses 17% less radiation along with the dual-energy features and is capable to provide similar objective image quality compared to the single-energy CT technique (12).

Because the evaluation of the vascularity via the measurement of the degree of contrast enhancement on CT images, reflects tumor angiogenesis, it can be used to predict metastasis and poor prognosis. In this study, we evaluated the presence of angiogenesis by determining the degree and the quantity of enhancement, the enhancement patterns, and iodine quantitation in lung nodules.

The first parameter that we evaluated in this evaluation was the contrast load; which required a quantitative assessment. According to the ROC analysis performed to quantify the contrast load in lung lesions, the cut-off density value of 19.25 HU was found to have sensitivity and specificity rates of 100% and 66.7%, respectively. The distribution of the contrast agent in malignant tumors and normal lung tissue is different. In order to nourish tissues; bronchial arteries grow, become tortuous, and ectatic. Furthermore, the clearance of the contrast agent from malignant tumors is limited. An already distributed contrast agent cannot be fully cleared from tissues because it has traversed into the extracellular area, too. This condition has been proven by many previous studies on dynamic contrast-enhanced CT showing that the contrast agent is not quickly washed out from malignant nodules (13). Similarly, we have observed false-positive results in some noduler lesion of infectious, inflammatory, pulmonary sequestration or vascular origin (such as arteriovenous malformations) due to the rapid accumulation of contrast in dynamic CT because of extensive vascular content. Therefore, the authors have proposed the best-fit combination theory using the three-minute delay following the administration of the contrast agent so that the high sensitivity in the differentiation of lung cancers could be sustained. It is known that the evaluation of tumor vascularity by measuring the degree of iodine contrast enhancement in lung nodules helps to distinguish malignant nodules from benign nodules in contrast-enhanced dynamic CT(14). However, dynamic methods are disadvantageous in terms of both the radiation dose and the cost-time efficiency.

It has been reported that early wash-out in dynamic contrast-enhanced Magnetic Resonance Imaging (MRI) has up to 95% sensitivity to indicate malignancy (14-15). However, this is another disadvantageous method in terms of long exposure protocols and costs associated with MRI. Furthermore, the efficiency of the method diminishes significantly in nodules smaller than 1 cm. A single contrast-enhanced CT scanning procedure in DECT provides additional information about the degree of contrast enhancement in the nodules without exposing the tissues to excessive doses of radiation.

The second parameter we investigated in our study was the quantitation of iodine in the lesion. According to this study measurements in the ROI in a nodular lung lesion, a cut-off value of 1.35mg/ml iodine can suggest whether the lesion is benign or malignant with 100% sensitivity and 67.7% specificity. In this study, the most appropriate threshold level was found as 1.35 mg/mL to determine the presence of contrast-enhancement with an iodine contrast agent. To date, no standards have been established for iodine concentration thresholds to help determine the presence of contrast or contrast enhancement in a lung nodule. A Previous study attempted to establish a calibration factor that would correlate the CT attenuation value (measured in HU) of a pulmonary nodule with the CT x-ray attenuation value (measured in mg/ml) and the iodine contrast agent concentration (measured in mg/ml). This study reported that values of 23.55 HU and 0.6 mg/mL would be ideal (16). In this study, we found a cut-off value of 19.25 HU for contrast load and 1.35 mg/ml for iodine load. Although these values are similar to those reported in the literature, they are associated with a higher iodine quantity and a higher sensitivity value compared to those reported by previous studies.

The third parameter we investigated in our study was the qualitative analysis of the changes in the color map on the image, depending on the increasing amounts of iodine in the lesion. With the advent of dual-energy CT, the visual assessment of iodine overlay color maps has made it possible to obtain additional information based on solely the presence of iodine, including the determination of iodine concentrations and the conduct of an attenuation analysis on a nodule.

According to the results of this study, one can suggest that it is still not clear whether the next diagnostic step in the management strategy should be to perform a biopsy or PET-CT imaging for nodules larger than 10 mm. Because DECT can detect contrast enhancement in the pulmonary nodules via both qualitative and quantitative methods, the results obtained by DECT and PET-CT are observed to be in parallel in determining the contrast enhancement and differentiating malignant lesions from benign ones. Therefore, DECT can be an alternative option to PET-CT in lesion characterization. The twin-beam technique used in obtaining the DECT scans in this study is notable because it causes less radiation exposure compared to other DECT techniques and the dynamic contrast-enhanced imaging techniques.

Furthermore, another point to receive attention in this study is the potential of using DECT as a method to evaluate the treatment response of metastatic lung nodules. In this study, we showed the simultaneous presence of active and necrotic nodules in the lungs of a previously treated patient; who was included in the study incidentally. A significant and apparent iodine load was present in the active metastatic nodule; whereas, the iodine quantity in the necrotic nodule was undetectable. Although only one case was observed, as a guide in this regard, we think that DECT may be an alternative follow-up imaging method that can be preferred as an alternative to PET-CT.

This study has some limitations that should be considered. Firstly, histopathological confirmations were not available for most benign nodules. Secondly, the quantitative distribution of the iodine load and the contrast load may be heterogeneous due to the relatively small number of patients included in the study. While planning the study, we assumed that the incidence of malignancy would increase in parallel to increases in the iodine load and the contrast load. Because of the exclusion of the nodules<6 mm, the results of smaller nodules could not be obtained. And although we exluded totally calcified nodules from the study, partially calcified nodules may increase false-positivity rate of both iodine and contrast calculations.

CONCLUSION

The diagnosis of pulmonary nodules is a challenge in clinical practice as they are very common in the general population. For the identification of malignant nodules, non-ınvasive imaging procedures are essential as lung biopsy may has sometimes severe complications. Evaluation of visual color evaluation, quantitative calculation of both iodine and contrast load on DECT technique as a non-invasive method, was found useful for the discrimination between malignant and benign pulmonary nodules. We think that further studies with a larger sample size are required to confirm the effectiveness of DECT on the differentiation of malignant and benign pulmonary nodules and also on the identification of other soliter parenchymal lung nodules.

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FİGURE LEGENDS

Figure 1. *The weighted average image (a), the virtual non-enhanced image (b), the iodine-enhanced image (c), and the image of the iodine load (d) are observed. The iodine component is shown as a color overlay on a background virtual non-enhanced image in the translucent mode (c-d).*

Figure 2. *Detection of calcification in the lung nodule on a virtual non-contrast-enhanced image.*
The weighted average image of the lesion in the apical segment of the left lung (a), the virtual non-contrast-enhanced image showing a small calcification around the nodule (white arrow) (b), dual view (c), and iodine load are shown. No significant 18-FDG uptake was observed in the PET-CT images obtained from the same patient (e).

Figure 3. *The weighted average image (a), the virtual iodine-enhanced dual image (b), and the image of the iodine load (c) are shown. A solitary pulmonary nodule with an infinitesimal contrast load and with an iodine load of 0.2mg/dl. The diagnosis was confirmed as a hydatid cyst* by a histopathological examination.

Figure 4. *A malignant nodule is shown on an iodine-enhanced image. Images showing the weighted average image (a), a virtual non-enhanced image (b-c), and the iodine load (d). In the iodine-enhanced image (d) the iodine value was found as 11.4mg/dl. The malignant characteristics of the nodule were confirmed clinically and via a PET-CT examination(e).*

Figure 4e. *The PET-CT image of the patient; whose Dual-CT images were presented above.*

Figure 5. *A benign lung nodule is shown on an iodinated image.*
The weighted average axial image (a), an image with no contrast load (b), the virtual iodine-enhanced image (c), and the iodine load (d) are shown. Solitary pulmonary nodule with no contrast load (b) diagnosed as a benign hamartoma.

Figure 6. *A benign lung nodule is shown on an iodinated image.*
The weighted average coronal (a), axial (b), virtual enhanced iodinated image (c), and the iodine load (d) are shown. A benign solitary pulmonary nodule, where the contrast load is infinitesimal. The solitary pulmonary nodule remained stable in the two-year follow-up period.

Figure 7. *Confirmed metastatic lung nodules originating from colon cancer are shown on the iodine-enhanced image of the patient presenting with shortness of breath. The weighted average image (a), the virtual iodine-enhanced image (b), and the image of the iodine load (c) are shown.*
On a weighted average image, it is difficult to determine whether the metastatic nodule responds to chemotherapy or not. However, it is easier to identify active and necrotic nodules by inspection on

iodinated dual images. The detection of the iodine load as 59.4mg/ml in the active nodule and as negative values in the necrotic nodule are the supporting findings.