Original Article

Dual-energy spectral CT in assessment of pleural effusion

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Abstract

Background: Pleural effusion is a common clinical problem. The ability to differentiate between benign and malignant pleural effusions has many clinical benefits. However, few studies have investigated the diagnostic value of dual-energy spectral computed tomography (DECT) in pleural effusion.

Objective: To evaluate the diagnostic values of DECT for assessment of pleural effusion.

Materials and Methods: We retrospectively analyzed data from 87 patients presenting with pleural effusion who underwent chest DECT from October 2019 to November 2020. Two reviewers blindly reviewed the CT images of pleural effusion in consensus. The pleural fluid attenuation in standard conventional CT images and monoenergetic images, at 40 keV, 100 keV and 140 keV, were recorded.

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Data pertaining to the effective atomic number, the iodine concentration (IC) and associated CT findings including pleural thickening, pleural nodules and extrapleural fat clouding was analyzed.

Results: Of 87 patients, 44 were presented with benign effusions and the remaining 43 were presented with malignancy. There were no statistically significant differences in differentiating between benign and malignant pleural effusions by using the attenuation values, the effective atomic number or the IC. Irregular pleural thickening and pleural nodules were detected statistically significantly in the patients with malignant pleural effusions with moderate accuracy, (48.83%; $p < 0.01$; AuROC 0.7103 and 34.88%; $p < 0.01$; AuROC 0.654 respectively).

Conclusion: DECT attenuation values did not show any reliable clinical value in the differentiation between benign and malignant pleural effusions. The presence of pleural nodules or irregular pleural thickening would suggest malignant pleural effusion with moderate accuracy.

Keywords: Pleural effusion, Dual energy spectral computed tomography, Benign pleural effusion, Malignant pleural effusion.

Introduction

Pleural effusion is a common clinical problem consequential to various benign and malignant causes including cardiac problems, malignant tumors, tuberculous pleuritis, and pneumonia. The pleural effusion can be classified into either transudate or exudate. Transudate effusions are caused by imbalances in capillary hydrostatic or colloid oncotic forces. The common causes are usually from cardiac or renal diseases such as heart failure, renal failure, and cirrhosis. However, an exudate effusion generally results from changes in the local factors influencing the accumulation of pleural fluid such as an increase in microvascular permeability, usually due to inflammatory or neoplastic processes [1, 2].

Differentiation between benign and malignant pleural effusions is important as this has an impact on the treatment decision and outcome. Early treatment of benign pleural effusion is curative and decreases the possibility of complications. Likewise, early diagnosis and treatment of malignant pleural effusion may improve the quality of life and increase the survival rate of patients [3].

Diagnostic thoracentesis is the first step in the characterization of a pleural effusion but the examination of pleural fluid cytology only has a sensitivity of about 60% for exclusion of malignancy; therefore, a video-assisted thoracoscopic surgery (VATS)-guided biopsy to confirm diagnosis may be required [1, 4]. However, the VATS is an invasive procedure. The combination of chest CT and pleural fluid cytology improves specificity and sensitivity for facilitating a differential diagnosis between benign and malignant pleural effusions [5].

Nowadays, recent innovations in CT technology have led to the introduction of dual energy spectral CT, the process becoming clinically applicable in enabling better discrimination and characterization of tissues. The dual energy spectral CT can differentiate between material densities by two different energies; low and high-energy images [6]. Dual energy spectral imaging can produce virtual monoenergetic images (40–140 keV) that reduce the beam hardening artifact that affects the CT number and provides a more accurate CT attenuation value than the conventional polychromatic X-ray [7, 8]. Many thousands of dual-energy spectral chest CT scans have been performed each year in our hospital. If dual-energy spectral chest CT can improve the accuracy in differentiation between the benign and malignant pleural effusions, it would be beneficial in avoiding invasive procedures, facilitating early diagnosis and treatment, subsequently improving the quality of life and increasing the survival rate among patients.

To the best of our knowledge, there are few studies investigating the diagnostic value of dual-energy spectral CT in pleural effusion. The objective of this study was to evaluate the diagnostic value of dual-energy spectral chest CT for assessment of pleural effusion.

THE ASEAN JOURNAL OF RADIOLOGY
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Materials and methods

2.1 Patients

This study was approved by the institutional review board and the written informed consent was waived because of the retrospective nature of the study. This study included 203 patients who underwent dual energy spectral CT of the chest or chest including the abdomen with presence of pleural effusion in our institution between October 2019 and November 2020. One hundred and sixteen patients were excluded from the study. The exclusion criteria were: (1) the nature of pleural effusion was undetermined (96.5%), (2) the amount of pleural effusion was too small to affect the measurement results (1.7%), (3) patients were younger than 18 years old (0.9%), and (4) patients were with unenhanced DECT scans (0.9%). Finally, 87 patients were enrolled into our study. Eligibility criteria for benign pleural effusion were: histopathologic or cytologic confirmation of negativity of malignancy, interval decreased amount of the pleural effusion after follow up imaging and no clinical scenario of malignancy. All of the malignant pleural effusions were verified by pleural fluid cytology or pleural biopsy.

2.2 Data collection and image analysis

All patients had undergone dual-energy spectral CT by using the 64-detector row SDCT system (iQon Spectral CT, Philips Healthcare). This system uses a single X-ray tube and a dual-layer detector. The detector separates the X-ray beam into low (upper layer) and high (lower layer) energy data, which is used to reconstruct spectral-based images (SBI). The SBI contain the raw data of both layers and are used to reconstruct any dual-energy images and/or facilitate analysis. The patients were in the supine position. The images were obtained in the craniocaudal direction. Fifty to one hundred ml (350 mg iodine/ml) of the contrast agent were injected through the antecubital vein at a dose of 1 ml/kg of the body weight, injected at a rate of 4.0-4.5 ml/sec. The portovenous phase of scanning was performed at 60-70 seconds after the injection of the contrast medium.

All CT images of pleural effusion were reviewed by two thoracic radiologists with consensus achieved. Post-processing reconstruction CT images use IntelliSpace Portal, version 9.0; Philips software workstation to evaluate the attenuation of pleural effusion in a pre-contrast scan, standard reconstruction conventional post contrast scan, 40 keV monoenergetic image, 100 keV monoenergetic image, 140 keV monoenergetic image, effective atomic number, iodine overlay (IO) image (Figure 1) and associated CT findings including pleural thickening, pleural nodules and extrapleural fat clouding (Figure 2). The pleural thickenings were classified into none, diffuse, irregular or circumferential thickening.

For the quantitative measurements, the area of the region of interest (ROI) ranging from 20 mm^2 to 70 mm^2 was placed in the center area of the pleural effusion and away from the artifacts (Figure 1). The copy-plate function was used in each patient to ensure equal localization and size. The pleural effusion of each patient has been measured three times in different location in each CT section and averaged to obtain the final result of mean value for attenuation and iodine concentration.

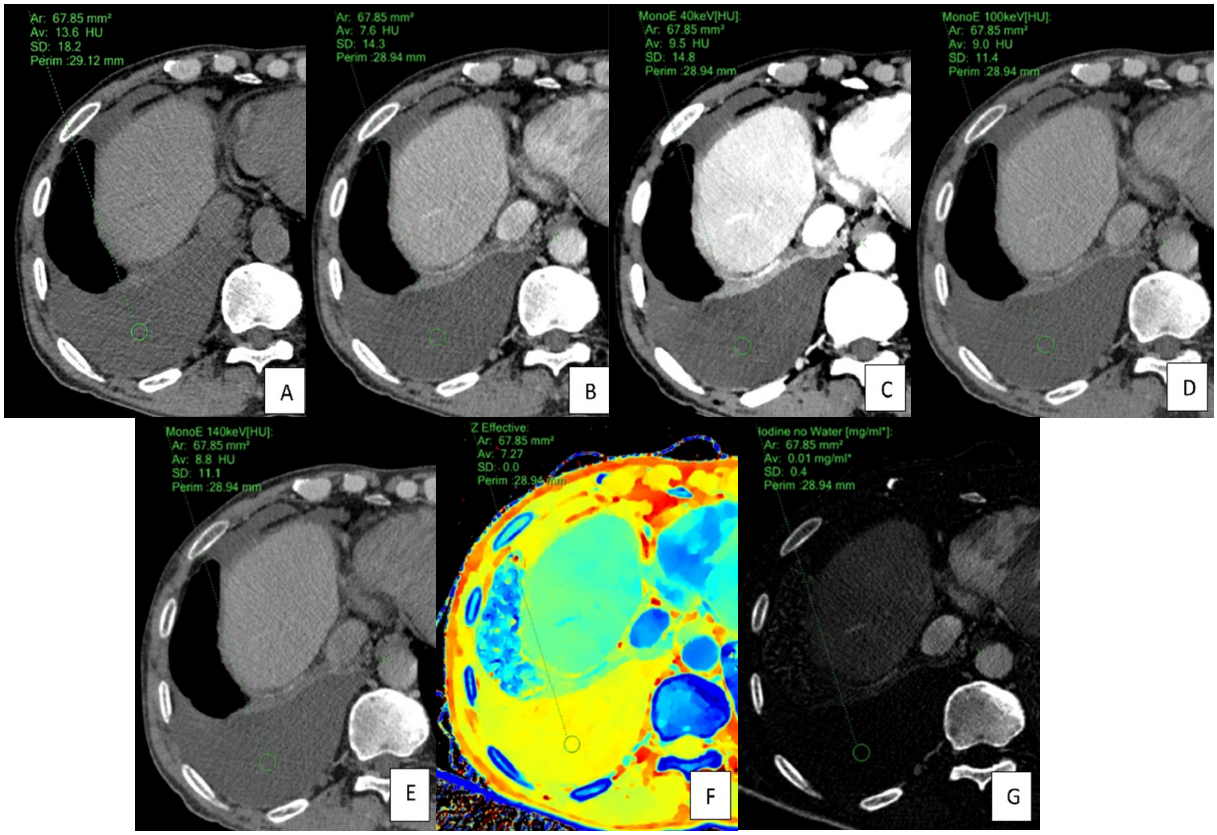

Figure 1. *ROI size and location in different images A: pre contrast scan B: standard reconstruction conventional post contrast scan C: 40 keV monoenergetic image D: 100 keV monoenergetic image E: 140 keV monoenergetic image F: effective atomic number G: iodine overlay (IO) image.*

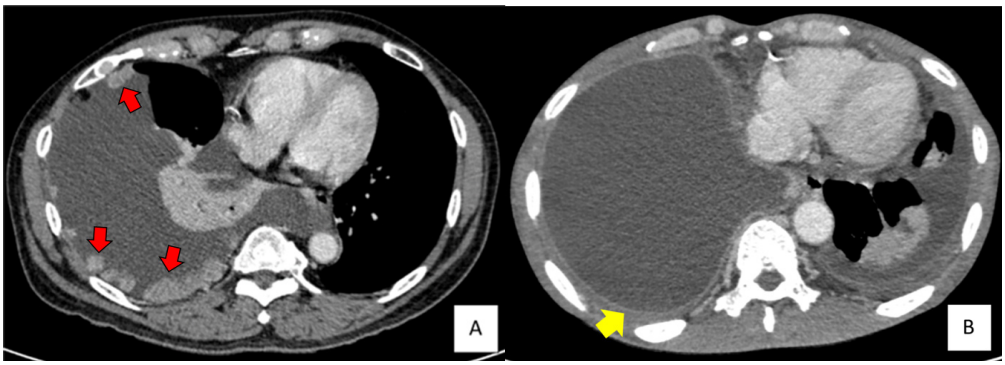

Figure 2. *Standard reconstruction chest CT images show multiple enhanced pleural nodules (red arrows) (A) and extrapleural fat clouding (yellow arrow) (B).*

2.3 Statistical analysis

Data was statistically analyzed using a programming package for statistics. The results were presented as mean and standard deviation for quantitative variables. Multiple logistic regression analysis was used to compare the various CT findings between benign and malignant pleural effusions. The independent sample student-t test was used to analyze the CT parameters including pre contrast scan, standard reconstruction conventional post contrast scan, 40 keV monoenergetic image, 100 keV monoenergetic image, 140 keV monoenergetic image, effective atomic number, iodine overlay image and associated CT findings including pleural thickening, pleural nodules and extrapleural fat clouding. Factors found to have a p-value < 0.05 in the initial analyses were included in the receiver operating characteristic (ROC) analysis. The ROC curves were generated to distinguish benign and malignant pleural effusion. Diagnostic capability was determined by calculating the area under the ROC curve (AuROC). All statistical analyses were performed using SPSS program version 25.

Results

Our study included 87 patients, divided into two categories including ones with benign effusion and ones shown with malignant effusion groups. The benign group included 44 patients, of whom, 26 were males and 18 were females with an age range of 33 to 79 years (mean age 61.04±11.6 years). The malignant group included 43 patients, of whom, 17 were males and 26 were females with an age range of 32 to 92 years (mean age 65 ±12.2 years). The demographic data of these patients is shown in Table 1.

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Table 1. *Demographic data of patients.*

Variable	Benign pleural effusion	Malignant pleural effusion	Total
Patients n (%)	44 (50.57)	43 (49.43)	87 (100)
Mean age years (SD)	61.04 (11.6)	65 (12.2)	63 (12.0)
Gender			
Female	18	26	44
Male	26	17	43
Causes of pleural effusions n (%)	TB pleurisy 6 (13.6) Bacterial empyema 7 (15.9) Heart disease 4 (9.1) Unidentified cause 27 (61.4)	Metastatic lung cancer 31(72.1) Metastatic breast cancer 5 (11.6) Metastatic stomach cancer 3 (7.0) Metastatic other tumors 3 (7.0) Primary malignant mesothelioma 1 (2.3)	87 (100)

SD, standard deviation.

3.2 Measurements from spectral CT between benign and malignant pleural effusions

In our study spectral CT based imaging showed no statistically significant difference regards to differentiation between benign and malignant pleural effusions by using the monoenergetic images at every energy level (21.75±11.06 HU vs. 21.37±11.05HU at 40keV, p = 0.873; 13.99±8.55 HU vs. 13.01±5.65 HU at 100keV, p = 0.528; 13.41±8.74 HU vs. 12.40±5.63 HU at 140keV, p = 0.520). Moreover, the standard conventional CT images showed no significant difference between the attenuation values between the benign and malignant pleural effusions in both pre- and post-contrast images (10.79±8.0 HU vs. 12.71±5.33 HU in pre contrast image, p = 0.206; 14.45±7.74 HU vs. 13.45±6.78 HU in post

contrast image, p = 0.523). No significant difference was found in the Z effective atomic number and the iodine concentration for differentiation between the benign and malignant groups (7.32±0.09 vs. 7.33±0.07 of the Z effective atomic number, p = 0.777; 0.13±0.09 vs. 0.12±0.10 mg/ml of the iodine concentration, p = 0.272). A summary of the measurement results is summarized in Table 2. The ROC analysis shown in Figure 3 indicates the inability to differentiate between benign and malignant pleural effusions in all measurement parameters.

Table 2. *Comparison of measurements from spectral CT between benign and malignant pleural effusions.*

Parameter	Benign (N=44) Mean (±SD)	Malignancy (N=43) Mean (±SD)	p-value	AuROC (Std.error)
Monoenergetic image (HU)				
40 keV	21.75 (±11.06)	21.37 (±11.05)	0.873	0.498 (0.065)
100 keV	13.99 (±8.55)	13.01 (±5.65)	0.528	0.497 (0.066)
140 keV	13.41 (±8.74)	12.40 (±5.63)	0.520	0.499 (0.066)
Pre contrast conventional image (HU)	10.79 (±8.0)	12.71 (±5.33)	0.206	0.623 (0.062)
Post contrast conventional image (HU)	14.45 (±7.74)	13.45 (±6.78)	0.523	0.466 (0.064)
Effective Atomic Number	7.32 (±0.09)	7.33 (±0.07)	0.777	0.517 (0.065)
Iodine concentration (mg/ml)	0.13 (±0.09)	0.12 (±0.10)	0.272	0.465 (0.065)

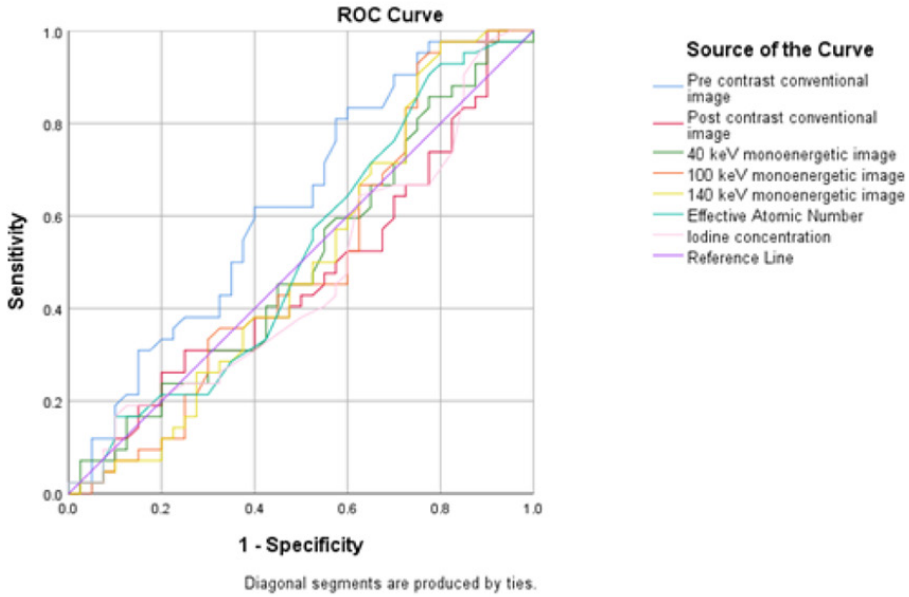

Figure 3. *The receiver operating characteristic curve of spectral CT parameters for differentiation between benign and malignant pleural effusions.*

Twenty-five out of 44 benign effusions had no pleural thickening (56.81%) while 14 out of 43 malignant effusions had no pleural thickening (32.55%) ($p = 0.023$). Pleural nodules were observed in 15 out of 43 malignant pleural effusions (34.88%) compared with 2 out of 44 benign pleural effusions (4.54%) ($p < 0.001$) (Figure 4). Of the 44 benign effusions, three showed irregular pleural thickening (6.81%) compared with 21 out of 43 malignant effusions (48.83%) ($p < 0.001$) (Figure 5). A summary of the associated CT findings between benign and malignant pleural effusions is shown in Table 3. There were no significant differences in diffuse pleural thickening, circumferential pleural thickening and extrapleural fat clouding between the two groups. The ROC analysis of pleural nodule and irregular pleural thickening revealed moderate accuracy in differentiating between benign and pleural effusions (AuROC 0.654 and 0.713 respectively) (Figure 6). The multivariate analysis of a combination of pleural nodules and irregular pleural thickening showed slightly increased accuracy in enabling the differentiation between benign and pleural effusions (AuROC 0.761 and standard error 0.053) (Figure 7).

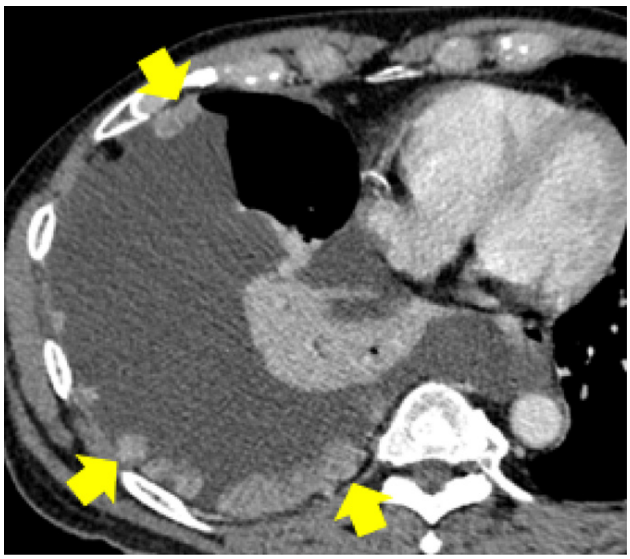

Figure 4. *A 66-year old man with lung cancer and right pleural metastasis-standard reconstruction chest CT images show multiple various size enhanced pleural nodules along the right hemithorax (arrows). Also noted large amount of right pleural effusion with adjacent compressive atelectasis of the right lower lobe. atelectasis of the right lower lobe.*

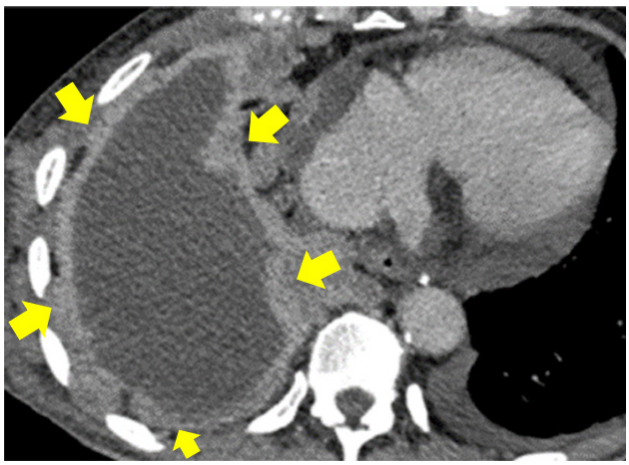

Figure 5. *A 70-year-old man with squamous cell lung cancer and right pleural metastasis-standard reconstruction chest CT images show right pleural effusion with subadjacent irregular pleural thickening along the right hemithorax (arrows).*

Table 3. *Comparison of the associated CT findings between benign and malignant pleural effusions.*

CT findings	Benign n=44 n (%)	Malignant n=43 n (%)	p-value	AuROC (Std.error)
Pleural thickening				
No thickening	25 (56.81)	14 (32.55)	0.023	0.367 (0.062)
Diffuse	8 (18.18)	11 (25.58)	0.404	0.556 (0.064)
Irregular	3 (6.81)	21 (48.83)	< 0.001	0.713 (0.058)
Circumferential	10 (22.72)	8 (18.60)	0.635	0.470 (0.064)
Pleural nodule	2 (4.54)	15 (34.88)	< 0.001	0.654 (0.061)
Extrapleural fat clouding	6 (13.63)	7 (16.27)	0.73	0.521 (0.064)

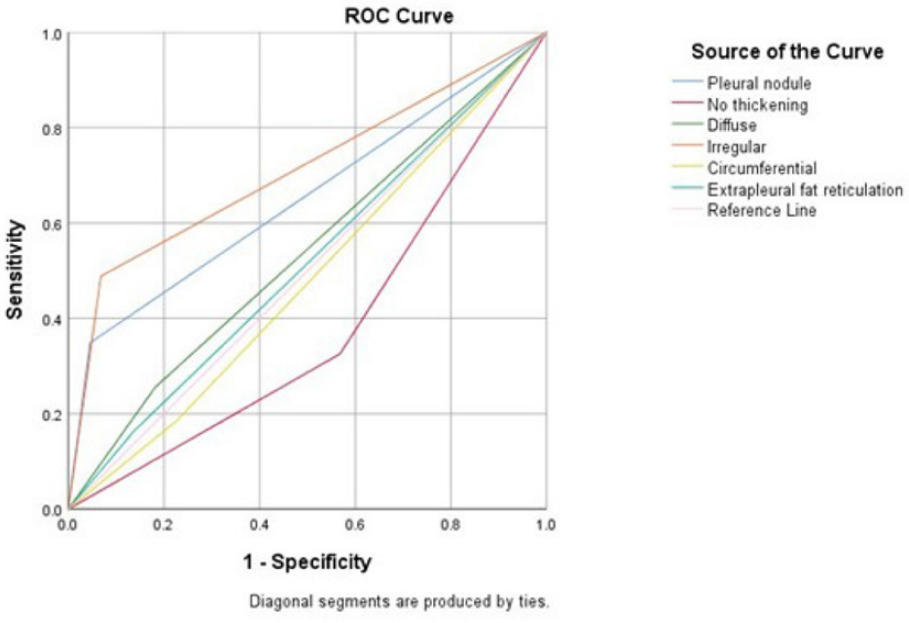

Figure 6. *The receiver operating characteristic curves of the associated CT findings for facilitating differentiation between benign and malignant pleural effusions.*

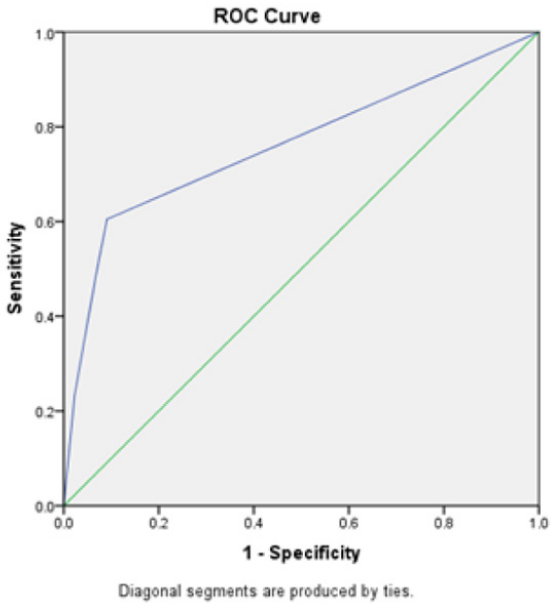

Figure 7. *The receiver operating characteristic curve for findings (combining irregular pleural thickening and pleural nodule) facilitating differentiation of malignant pleural effusion from benign pleural effusion (AUC 0.761 and Std. error 0.053).*

Discussion

In our study, the pleural fluid attenuation values on DECT had no significant role in characterizing pleural effusions as benign or malignant etiologies. The mean CT attenuation values in this study were about the same for both groups of effusion in the standard conventional CT images and even between the monoenergetic images at every energy level. The mean attenuation values ranged from 10-22 HU and did not accurately differentiate between benign and malignant pleural effusions in our study. Some other previous studies also claimed that CT attenuation value was found to be a moderate to poor indicator for characterization of effusions [1, 9]. The increased attenuation of the effusion potentially depends on the levels of protein, lactate dehydrogenase (LDH), bilirubin, haemocytes and hemoglobin which are the more prevalent components of malignant effusions in comparison

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with benign effusions [10]. However, some benign effusions such as the tuberculous effusions are commonly exudates and invariably contain protein concentrations >30 g/L in up to 77% of cases. Additionally, The LDH level of tuberculous pleural fluid is elevated in approximately 75% of cases, with levels frequently exceeding 500 IU/L [11]. Hamm et. al. [12] found that the elevated pleural cholesterol in malignant effusions is possible due to major cellular degeneration or increased pleural permeability. Consequently, the high cholesterol level, which reduces the attenuation may degrade the expected high CT attenuation values in malignant effusions. These lead us to infer that no significant difference of the mean attenuation values between benign and malignant effusions because of the overlapping attenuation values. However, Zhang et. al. [3] reported that CT attenuation values between the benign and malignant pleural effusions were statistically different in 40keV and 100keV monoenergetic spectral images (43.15±3.79HU vs. 39.42±2.60HU at 40keV, $p = 0.005$; 9.11±1.38HU vs. 6.52±2.04HU at 100keV, $p<0.001$). One possible explanation may be due to the small sample of patients in the study (14 patients with benign pleural effusion and 15 patients with malignant pleural effusion). The mean attenuation values of their study were notably similar in both groups of effusion, which means it would be difficult to apply the findings of these examinations in the clinical use of CT numbers to differentiate pleural fluid.

Z-effective images are the color-coded images based on the effective atomic number of tissues. The coefficients of the photoelectric and Compton scatter components computed during the spectral decomposition process are as a result of influences of the spatial distribution of tissues [13]. The effective atomic number provides a better discrimination than the attenuation values because it displays the material make-up of each pixel [14]. However, our study revealed almost identical effective atomic numbers and iodine concentrations between malignant and benign effusions. These show a correlation with the results of the CT attenuation value and may imply that there is no association between the effective atomic number or the iodine concentration and the type of pleural effusions.

Many studies have proposed that the conventional chest CT can be used to differentiate between benign and malignant pleural effusions by using the imaging characteristics such as pleural nodularity, pleural nodules and pleural thickening [15-20]. Our study found that irregular pleural thickening and pleural nodules were detected at a statistically significant level in the patients with malignant pleural effusions, (48.83%; $p < 0.001$ and 34.88%; $p < 0.001$ respectively). However, the overall accuracy of the use of irregular pleural thickening and pleural nodule to differentiate between benign and pleural effusions was only moderate (AuROC 0.713 and 0.654, respectively). Overall, these findings are in accordance with findings reported by Yilmaz U et. al. [17] who reviewed 146 patients with proven pleural disease. This team reported that pleural nodularity and irregular pleural thickening greater than 1 cm were helpful in distinguishing malignant from benign pleural diseases. The findings of this study are similar to those reported by Leung et. al. [18] which published that nodular pleural thickening had a high specificity (94%) for the diagnosis of malignant pleural disease. A study by Maffessanti et. al. [21] suggested that the absence of pleural thickening does not preclude malignant effusion because 7 out of 12 patients with malignant effusions in that series had normal-appearing pleura. Similar to these findings is our study which found that about one-third of the malignant group had no pleural thickening.

There were some limitations to our study. First, it is retrospective in nature; therefore, the data may not be as standardized as other types of study, and the thoracentesis and DECT were not performed at the same time in some patients. Second, we defined the mean HU using only three axial slices despite the variation in the volume of fluid. It is possible that volume averaging might play a larger role in smaller effusions making attenuation values less accurate. Finally, we determined the results from only one CT scanner vendor's hardware and software application.

Conclusion

In conclusion, dual-energy spectral CT attenuation values did not demonstrate reliable clinical values in enabling the differentiation between benign and malignant pleural effusions. Associated pleural CT appearance features including pleural nodule and irregular pleural thickening would suggest malignant pleural effusion with moderate accuracy.

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