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Pleural plaques and pleural changes among lung cancer patients exposed to asbestos

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ABSTRACT

BACKGROUND
Indonesia is one of the world's largest asbestos importing countries. While asbestos is the main contributor to work-related lung cancer, studies or reports regarding the CT findings of asbestos-related lung cancer have been limited in the country. The objective of this study was to compare CT findings of the size of the tumor and pleural and lung parenchymal changes between lung cancer patients exposed to asbestosis and those not exposed.

METHODS
This cross-sectional study involved 96 lung cancer patients consisting of 48 subjects who had been exposed to asbestos and 48 who had not been exposed. They underwent thoracic CT scans at the Radiology Department of Persahabatan Hospital. Asbestos exposure was determined using interviews that followed a protocol similar to that of a previous study about asbestos-related lung cancer. Senior radiologists investigated the existence of pleural and parenchymal changes. An independent T-test and chi-square test to compare CT scan features between the two groups.

RESULTS
The mean age was 57.75 ± 8.56 years in the asbestos-exposed group and 58.56 ± 7.99 years in the unexposed group. The proportion of tumor sizes of more than five cm, pleural plaques, and subpleural dot-like or branching opacities were significantly higher among asbestos-exposed subjects compared to the non-exposed group (p=0.044; p=0.37; p=0.041, respectively).

CONCLUSIONS
Asbestos exposure is significantly related to the size of the tumor and the existence of pleural plaques and asbestosis. These findings may help further management of lung cancer patients and the policy of asbestos use in Indonesia.

Keywords: Pleural plaque, asbestosis, lung cancer, asbestos, adults

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INTRODUCTION

Lung cancer is the most commonly diagnosed cancer in men and the leading cause of cancer death worldwide. In Indonesia, lung cancer ranks first in men and third in both sexes in terms of incidence, with 34,783 new cases and accounting for 30,843 deaths in 2020.[1]

Even though the cause of lung cancer is mainly attributed to tobacco smoking, other agents also play a role in lung cancer.[2] Studies found that the incidence of lung cancer also rises among non-smokers, indicating that environmental and occupational exposure to other agents contribute to lung cancer as the world is becoming more industrialized.[3] Asbestos, radon, and arsenic are widely known non-tobacco carcinogens associated strongly with lung cancer.[2,4,5] Occupational exposure contributes 17% to 29% of all lung cancers in men. Out of all work-related lung cancers, asbestos has been proclaimed the primary contributor, responsible for around 85% of all occupational deaths.[6] According to the World Health Organization (WHO), at least 125 million workers are exposed to asbestos in the workplace, and 107,000 people die each year from asbestos-related diseases.[7]

Asbestos is a group of natural fibrous minerals that can cause a spectrum of benign to malignant pulmonary diseases, such as asbestosis, pleural fibrosis and plaques, benign asbestos pleural effusion, and malignant mesothelioma, besides lung cancer.[8] Asbestos gained popularity in the late nineteenth century due to its fireproof and insulation properties. It was widely used for commercial applications, predominantly in the construction industry throughout the twentieth century.[9] At present, around 65 countries have completely banned all forms of asbestos.[10] Unfortunately, the use of asbestos is increasing in Eastern Europe, Asia, and South America.[11] Indonesia has imported asbestos since 1950 and is currently one of the world's largest importers of asbestos, after India and China.[12]

The most common asbestos-related malignancy with high mortality is lung cancer.[13] Chest CT is the best imaging modality to diagnose lung cancer. It can also detect abnormalities in the lung parenchyma and pleura, such as pleural plaques or diffuse pleural thickening, likely to be found in individuals with asbestos exposure.[14,15] Several studies showed that pleural plaques are early manifestations of asbestos exposure, and that asbestos exposure is associated with an increased risk of malignancies. Therefore studies on CT imaging of asbestos-related lung cancers have been conducted in various countries.[16–19] Lung cancer caused by asbestos exposure is not always preceded by asbestosis. The presence of asbestosis and pleural plaques on CT imaging of lung cancer patients may suggest the possibility of asbestos exposure as the cause of cancer. Therefore, it should not be ignored. However, a case report on the risk of lung cancer and radiology imaging in a construction worker have proved the existence of asbestos-related lung cancer in Indonesia.[20] Some studies evaluated the tumor location or histopathological type of lung cancers in asbestos-exposed and unexposed patients.[21] Several studies have also demonstrated an increase in lung cancer risk, although no consistent dose-response relationship was observed while considering occupational exposure to specific lung carcinogens such as asbestos or silica.[22,23] Although there is still no uniformity of results, the majority of studies reported no significant difference between asbestos-exposed and unexposed lung cancers based on tumor location and histopathology. Therefore further research must be done. The objective of this study was to compare CT findings of tumor size and pleural and lung parenchymal changes between lung cancer patients exposed to asbestosis and those not exposed.

METHODS

Research design

A cross-sectional study analyzed the presence of asbestos-related parenchymal and pleural abnormalities and cancer morphology in

subjects who had histologically confirmed lung cancer. The study was conducted in Jakarta, Indonesia, from September 2020 to January 2021 at the Radiology Department of Persahabatan Hospital.

Research subjects

Subjects were recruited from secondary data of a previous study entitled "Asbestos-related lung cancer: A hospital-based case-control study in Indonesia".[5] The inclusion criteria were patients with primary lung cancer who had chest CTs and a clear history of asbestos exposure (exposed or unexposed). Asbestos exposure was considered to be positive if there was a history of occupational exposure to asbestos at least ten years prior to the interview. Subjects who had chemotherapy and incomplete data were excluded. A total of 48 subjects met the asbestos-exposure criteria, and 48 subjects with no history of asbestos exposure were enrolled as controls. Both groups were similar in age, sex, and smoking history.

Image interpretation

This study used 128-slice Siemens CT Scanner detector configurations with reference protocol, radiation dose of 80–160 mAs and 120 kVp tube current time, as well as gantry rotation time of 0.33–0.50 seconds. The images obtained were interpreted by a general radiologist from Indonesia and 2 thoracic consultant radiologists with more than 10-year experience from Germany.

The features of lung cancer assessed included size and margin of the mass, enlarged lymph nodes, and metastases, based on the eighth edition of the TNM staging system.[24] The pleural abnormalities assessed were pleural effusion, pleural plaques, diffuse pleural thickening, and rounded atelectasis. Other lung parenchyma abnormalities evaluated were linear opacities and subpleural nodularities, curvilinear lines, parenchymal bands, interstitial intralobular thickening, interlobular septal thickening, ground-glass opacities, and honeycomb appearance.[25]

Statistical analysis

The data were processed using the Statistical Package for the Social Sciences (SPSS) version 25. Univariate analysis was carried out to describe the characteristics of the research subjects, including age, gender, CT findings of lung cancer characteristics. Categorical data were presented as proportions while numerical data were presented as mean and standard deviation. Using the independent -T-test and chi-squared test, bivariate analysis was done to compare CT scan features between asbestos-exposed and unexposed lung cancer.

Ethical clearance

The ethics committee of Persahabatan Hospital has approved this study under No. 18/KEPK-RSUPP/03/2018.

RESULTS

Almost all subjects were male (97.2%), with mean age of 57.75 ± 8.56 years in the asbestos-exposed group and 58.56 ±7.99 years in the unexposed group. The commonest smoking history for both asbestos-exposed and unexposed groups was 501 to 1,000 pack-years. The distribution of smoking rate is shown in Table 1.

In asbestos-exposed subjects, it was found that the tumor mass was more likely to be found in the right lung (58.3%), upper lobe (52.1%), and central (66.7%) in location. The mass was mostly more than 7 cm (60.4%) and had regular edges (62.5%). Ipsilateral mediastinal and subcarinal lymph node enlargement (N2) was the most typical (16.3%). Metastasis was primarily found in the lung (20.8%). Other conditions caused by the tumors such as rib fracture were seen in 6.25% of patients and pleural effusion in 52% of patients. The comparison of the tumor mass imaging characteristics between the exposed and unexposed groups is shown in Table 1. There was a significant difference in tumor size in which the proportion of tumor sizes of 5–7 cm and >7 cm was higher in the asbestos-exposed group (p=0.044).

Table 1. Selected characteristics on Chest CT of the study subjects by asbestos exposure

	Asbestos exposure		p value*
	Exposed (n=48) n (%)	Unexposed (n=48) n (%)	
Age (years) [Mean ± SD]¶	57.75 ± 8.56	58.56 ± 7.99	0.623
Sex			1.000
Male	47 (97.92)	47 (97.92)	
Female	1 (2.08)	1 (2.08)	
Smoking history (pack-years)			
0 – 200	9 (18.8)	10 (20.8)	
201 – 500	13 (27.1)	12 (25)	0.992
501 – 1.000	20 (41.7)	21 (43.8)	
1001 – 1.500	4 (8.3)	3 (6.3)	
>1501 – 2.000	2 (4.2)	2 (4.2)	
Tumor location			
Location A			
Right	28 (58.3)	31 (64.6)	0.529
Left	20 (41.7)	17 (35.4)	
Location B			
Superior	25 (52.1)	27 (56.25)	0.436
Inferior	14 (29.2)	12 (25)	
Medially/lingula	1 (2.2)	4 (8.33)	
Multiple lobes	8 (16.7)	5 (10.41)	
Location C			
Peripheral	16 (33.3)	12 (25)	0.369
Central	32 (66.7)	36 (75)	
Size (cm)			
< 3	4 (8.3)	4 (8.33)	0.044
3 -5	4 (8.3)	14 (29.16)	
5 -7	11 (22.9)	5 (10.41)	
> 7	29 (60.4)	25 (52.08)	
Edge			
Regular	30 (62.5)	26 (54.2)	0.408
Irregular	18 (37.5)	22 (45.8)	
Lymph node enlargement			
N1	2 (4.2)	1 (2.1)	0.873
N2	16 (33.3)	15 (31.3)	
N3	5 (10.4)	7 (14.6)	
Metastasis			
Lung	10 (20.8)	11(22.9)	0.749
Pericardial effusion	6 (12.5)	7 (14.6)	
Lung and pericardial effusion	4 (8.3)	3 (6.2)	
Others	2 (4.2)	1 (2.1)	

Data presented as n (%) except for age (Mean ± SD); * Chi-squared test was used for categorical variables; ¶ Independent-t-test

The histological features of the lung cancers in all subjects can be seen in Table 2. The most common type of cancer found in this study was adenocarcinoma. Using the chi-squared test, there was no significant difference in histological type between the two groups of subjects.

Figure 1 and Figure 2 present the pleural and the lung parenchyma abnormalities on CT of asbestos-exposed subjects and Table 3 describes the proportion of these abnormalities in both asbestos-exposed and unexposed groups. The proportion of pleural effusion in both groups of subjects was identical. Diffuse pleural thickening and pleural plaque were more frequent in the exposed group ($p<0.05$). Among pulmonary parenchymal abnormalities related to asbestosis,

Table 2. Comparison of histological features of lung cancer in asbestos-exposed and unexposed subjects

	Asbestos exposure		p-value *
	Exposed n (%)	Unexposed n (%)	
Non-small cell carcinoma			
Squamous cell carcinoma	14 (29.2)	13 (27.1)	
Adenocarcinoma	16 (33.3)	17 (35.4)	
Large cell carcinoma	1 (2.1)	0	
Others	1 (2.1)	2 (4.2)	0.843
Small cell carcinoma	0	2 (4.2)	
Neuroendocrine carcinoma	0	1 (2.1)	
Unidentified	16 (33.3)	13 (27.1)	

* Chi-squared test was used for categorical variables

the proportions of parenchymal bands, subpleural dot-like or branching opacities, and subpleural curvilinear lines were significantly higher in the asbestos-exposed group.

DISCUSSION

Several studies on CT imaging of asbestos-related lung cancers have been conducted in various countries.[16-19] Some studies evaluated the tumor locations or histopathological type of lung cancers in asbestos-exposed and unexposed patients and although there is still no uniformity of results, the majority of these studies reported no significant difference between asbestos-exposed and unexposed lung cancers based on tumor location and histopathology. Lung cancer caused by asbestos exposure is not always preceded by asbestosis. However, asbestosis may be associated with an increased risk of lung cancer due to fibrotic reaction.[26]

This study provides an overview of differences in CT scan findings between asbestos-exposed and unexposed lung cancer patients. Parenchymal and pleural changes such as pleural plaques, parenchymal bands, subpleural dot-like or branching nodularities, and subpleural curvilinear lines are significantly found in

Table 3. Comparison of pleural and lung parenchymal abnormalities on chest CT in asbestos-exposed and unexposed lung cancer patients

	Asbestos exposure		p-value *
	Exposed n (%)	Unexposed N (%)	
Pleural abnormality			
Pleural effusion	25 (52.1)	25 (52.1)	1.000
Diffuse pleural thickening	14 (29.2)	9 (18.8)	0.232
Pleural plaques	10 (20.8)	3 (6.3)	0.037
Pulmonary parenchymal abnormality			
Round atelectasis	0	0	-
Parenchymal band	11 (22.9)	4 (8.3)	0.049
Subpleural dot-like or branching opacities	4 (8.3)	0	0.041
Interlobular septal thickening	8 (16.7)	3 (6.3)	0.109
Intralobular interstitial septal thickening	5 (10.4)	2 (4.2)	0.239
Subpleural curvilinear lines	4 (8.3)	0	0.041
Traction bronchiectasis/bronchiectasis/ bronchiectasis	6 (12.5)	9 (18.8)	0.399
Honeycomb	1 (2.1)	0	0.315
Ground glass opacities	2 (4.2)	2 (4.2)	1.000

* Chi-squared test was used for categorical variables

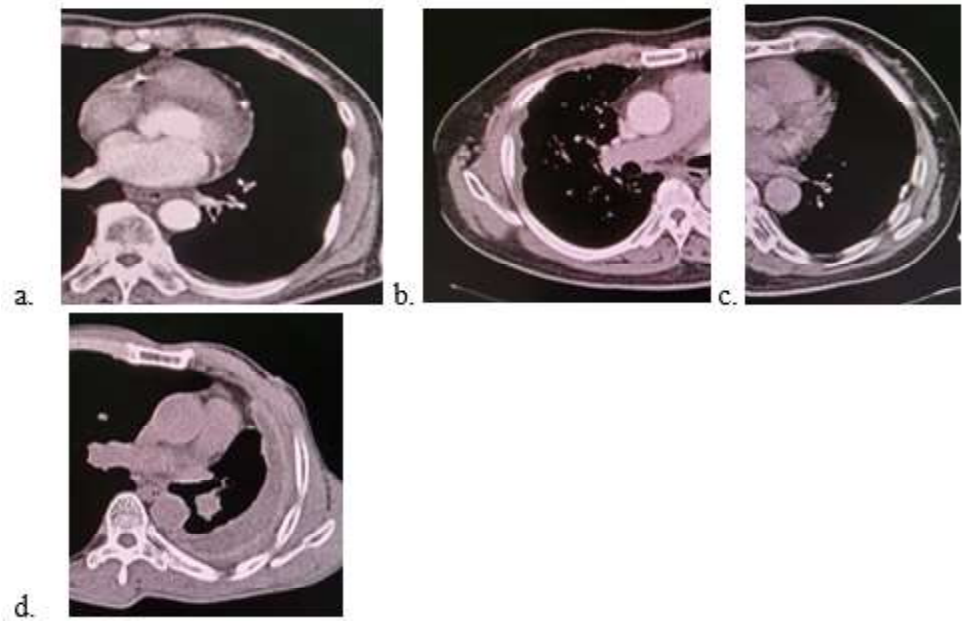

Figure 1. Pleural abnormalities found in the study subjects: pleural plaques (a,b), calcified pleural plaques (c), and pleural effusion with pleural thickening (d)

asbestos-exposed lung cancer patients. According to Cha et al.,[14] the most common parenchymal features in Korean patients with asbestosis are subpleural dot-like or branching opacities (97.5%), parenchymal bands (50.5%) and pleural plaques (98.5%). In the early stage of asbestosis, the high resolution CT findings include subpleural dot-like structures, subpleural lines, intralobular interstitial thickening, interlobular septal thickening, ground-glass opacities, and parenchymal bands.[27] This is in accordance with our study which found that parenchymal bands, subpleural nodularities, and subpleural curvilinear opacities were more frequent and statistically

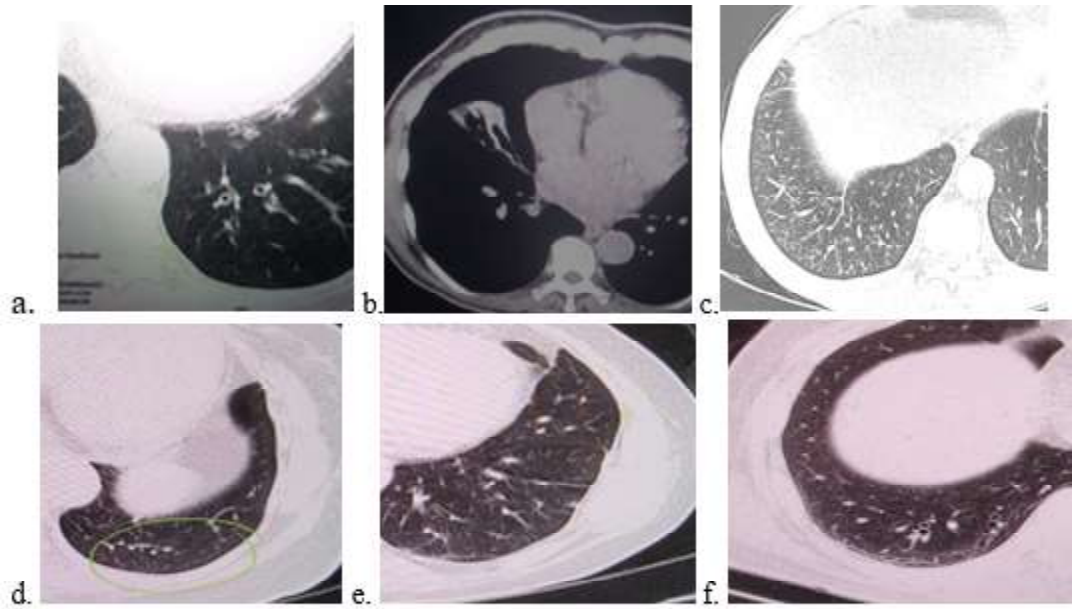

Figure 2. Lung parenchymal abnormalities found in the study subjects: bronchiectasis (a), traction bronchiectasis (b), thickening of interlobular and intralobular interstitial septa (c), nodular opacity/branching in the subpleura (d) and curvelinear lines (e, f)

more significant in the asbestos-exposed group. Asbestosis is not necessarily found in asbestos-related lung cancer, but it is associated with an increased risk of lung cancer.[16,20] Detection of these abnormalities might indicate previous asbestos exposure and help radiologists assess the possibility of asbestos-related lung cancer. Therefore, these abnormalities should not be ignored.

Pleural plaque is considered a marker of asbestos exposure.[26] The presence of pleural plaque increases the risk of lung cancer. Therefore, the attribution of lung cancer to asbestos exposure has to be supported by occupational history.[28] Attention should be given particularly to individuals with a history of employment in the construction industry, as this sector has the highest prevalence of pleural plaques.[17]

Other parenchymal and pleural changes, namely interlobular septal thickening, interstitial intralobular septal thickening, traction bronchiectasis, honeycomb appearance, ground-glass opacity, pleural effusion, and diffuse pleural thickening were not significantly different in asbestos-exposed and unexposed groups. Those abnormalities can also be caused by other conditions, such as post-infection or interstitial pulmonary fibrosis (IPF).[14,29]

Pleural plaques occur more commonly in subjects with increasing time since first exposure to asbestos and with greater cumulative exposure, especially to amphibole varieties of asbestos.[30] Although cumulative asbestos exposure is associated with an increased risk of lung cancer, contradictory data from other studies raise questions as to whether subjects with pleural plaques have an additional higher risk of lung cancer.[31,32]

According to CT features in the lung cancer patients, the difference in tumor size between asbestos-exposed and nonexposed groups is statistically significant. To the best of our knowledge, there is no study reporting that tumor size in lung cancer is significantly associated with asbestos exposure. The findings of histological features in this study are in accordance with previous studies in which the major histological types of lung cancer are found in asbestos-exposed and nonexposed individuals with no significant differences.[19,,33] Therefore, histological type has no value in determining asbestos exposure in lung cancer.

Several features of the pleural and lung parenchymal abnormalities may be caused by other diseases such as tuberculosis which also causes fibrotic changes and is very common in Indonesia. Unfortunately, this study did not perform histopathological examination to exclude other possible causes. In order to overcome the issue, this study referred to existing studies that may explain those lesions.[14,29] In addition, all CT scans were interpreted by two senior radiologists who had more than ten years experience as a thoracal consultant.

The limitation of this study is that it was conducted in one center, although that center is a national referral hospital for lung disease in Indonesia. In Indonesia there is a lack of studies such as the present study and as far as the author knows, this is the first study so it cannot be compared to other studies. Further studies are needed and it would be better if these studies were conducted in multiple centers because it would better represent the population.

CONCLUSIONS

This study revealed that the proportions of pleural plaques and asbestosis are significantly higher in asbestos-exposed lung cancer subjects than in the nonexposed ones. These findings may help further management of lung cancer patients and the policy of asbestos use in Indonesia.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to the subject matter discussed in this manuscript.

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AUTHOR CONTRIBUTIONS

Conceptualization and methodology AGI, CW, AS; data collection AS, AGI, CW, MF; data analysis AGI, CW, AS, MF; writing—original draft preparation, AGI, CW, AS; writing—review and editing AS, MF. All authors have read and agreed to the published version of the manuscript.

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