Original Article

Negative Chest Radiograph in Patients with Symptomatic Lung Cancer

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Objective: To evaluate the percentage of negative chest radiograph in patients with symptomatic lung cancer.

Materials and Methods: The authors retrospectively reviewed the chest radiographs of 263 patients with symptomatic lung cancer. The findings were divided into two categories and three subgroups, negative findings as normal, no abnormality detected or abnormal, or no cancer suspected, and positive findings as abnormal or cancer suspected. The recorded data included the tumor size, location, features of all lesions, the duration of symptom, and time intervals between the first chest radiograph until diagnosis. Computed tomography (CT) scan of the negative finding chest radiographs were reviewed to verify whether the causes of unsuspected malignancy were on a radiograph.

Results: Negative chest radiographs in the present study were 12.9%. Three patients (1.1%) were classified as entirely normal. Most findings in the abnormal, no cancer suspected group were patchy infiltration (8.4%), interstitial infiltration (1.9%), and thin wall lung cavity (1.1%). The major causes of negative findings were tumor location, size, conspicuity, obscured primary tumor, pulmonary tuberculosis mimicking lung cancer, and characteristic of lung cavity on the radiograph.

Conclusion: Negative chest radiographs can be found even in patients with symptomatic lung cancer, resulting in delayed diagnosis and treatment. Using chest radiograph as a first-line imaging investigation, especially in high-risk lung cancer patients, should be cognizant of false negatives.

Keywords: Lung cancer; Chest radiograph

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Lung cancer is one of the leading causes of death worldwide and has the highest rate of new cases and mortality[1,2]. In Thailand, lung cancer is the second leading cause of death after liver cancer, representing 22.2 cases per 100,000 individuals[3]. In 2020 alone, there were 20,395 deaths from lung cancer[4].

In developed countries, such as the United States and Europe, lung cancer screening guidelines have been set for people at high risk of lung cancer, using low-dose non-contrast chest computed tomography (CT) scans and Lung-RADS system reports, to detect lung cancer at an early stage and set monitoring practices. The screening was found to reduce the mortality rate[5,6]. However, there are still patients who are not participating in the screening.

Currently, there are no national guidelines for lung cancer screening with low-dose non-contrast chest CT scans in Thailand. Lung cancer patients may be detected when symptoms are present, or chest radiographs are performed for other reasons. Therefore, chest radiograph is still commonly used as the first-line investigation for lung cancer because of its affordability and accessibility.

Despite how it is easily accessible and commonly used, the sensitivity of lung cancer detection with chest radiographs in patients with symptoms of the disease is unclear. Therefore, the present study sought to determine the negative percentage of chest radiographs in patients with symptomatic lung cancer. The information provided from the present study would help understand the limitations of chest radiographs and allow better planning for patient treatment.

Materials and Methods

The authors retrospectively reviewed and collected data of patients with symptomatic lung

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cancer diagnosed between January 1, 2011 and September 30, 2020 at the author' institute. All patients must have respiratory symptoms or other non-specific symptoms of cancer, leading to investigation with a chest radiograph, such as hemoptysis, shortness of breath, chest pain, rib pain, shoulder pain, cough, hoarseness, loss of weight, fatigue, or loss of appetite. The present study was approved by the Ethics Committees of Faculty of Medicine, Vajira Hospital, Navamindhradhiraj University (COA 181/2563).

Two hundred sixty-three patients with symptomatic lung cancer whose first chest radiograph was relative at the time of symptoms with pathological confirmation of lung cancer were included in this study. Recurrent lung cancer, secondary lung malignancy, or other intrathoracic malignancies were excluded from the present study. Diagnosed lung cancer patients from the screening population were also excluded.

Over the course of the present study, retrospective series and various referring primary and secondary care centers, chest radiographs were performed by various machines. Two experienced radiologists with experience in lung cancer diagnosis reviewed and reached consensus on the chest radiographs. The findings were divided into two categories and three subgroups:

1) Negative findings:
   - Normal, no abnormality detected or
   - Abnormal, no cancer suspected
     • Patchy infiltration
     • Reticular infiltration
     • Reticulonodular infiltration
     • Thin wall cavity
2) Positive findings:
   - Abnormal, cancer suspected
     • Solitary pulmonary nodule
     • Pulmonary mass
     • Multiple pulmonary nodules
     • Golden S sign
     • Hilar mass
     • Apical pleural thickening
     • Widening mediastinum
     • Thick wall cavity
     • Pleural effusion (without any sign or clinical of volume excessive or infection)

The authors also recorded the size, location, and features of all lesions on the chest radiographs in which a patient might have more than one lesion. Additionally, data on the duration of symptoms and time interval from the first chest radiograph until definite diagnosis were collected. When a patient had a negative radiograph, the radiologists would review the CT scan to see whether there were any radiological features, location, or limitations causing the lesions not to be seen or there was unsuspected malignancy on the chest radiograph.

Statistical analysis

Patients' characteristic data were summarized using descriptive statistics. Continuous data were presented as mean ± standard deviation (SD) or median (range), and categorical data were presented as frequency and percentage. The differences in clinical symptom presentation between chest X-ray results as normal finding, abnormal findings but no cancer suspected and positive findings, were compared using chi-square test. Analyses were performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Two hundred sixty-three lung cancer patients were included in the present study. The mean±SD age of patients was 62.6±11.2 years, and 55.5% were men. The top three most common clinical symptom presentations were cough (57.8%), dyspnea (26.6%), and weight loss (26.2%), respectively. Most of the patients were diagnosed with adenocarcinoma (75.5%). There were no available histological subtype data in 14 patients with non-small cell carcinoma.

Table 1 shows the details of patient's characteristics of the study.

Table 2 shows the chest radiograph results of patients with symptomatic lung cancer. Observed positive findings for lung cancer in chest radiographs were 87.1% (95% CI 84.4 to 90.9). The negative chest radiograph was 12.9%. Three patients (1.1%) were classified as entirely normal.

Table 3 summarizes the frequencies for each chest radiograph findings. The most common chest radiograph findings in "abnormal, no cancer suspected group" were patchy infiltration (8.0%). The CT findings of these patchy infiltrations were consolidation (36.4%), pulmonary mass (22.7%), mass in the collapsed lung (18.2%), and endobronchial mass with lung atelectasis (9.0%). Pulmonary mass was the most common finding (47.9%) in "positive findings group" followed by hilar mass (14.1%) and solitary pulmonary nodule (8.4%). Mean tumor or lesion size (±SD) in the positive chest radiograph was 5.57±2.64. Right upper lobe was the most site of tumor location at 25.1%.

Table 1. Characteristic data of lung cancer patients

Characteristic	n=263
Age (years); mean±SD (range)	62.6±11.2 (35, 89)
Sex; n (%)	
Male	146 (55.5)
Female	117 (44.5)
Clinical presentation; n (%)	
Cough	152 (57.8)
Dyspnea	70 (26.6)
Weight loss	69 (26.2)
Chest pain	44 (16.7)
Hemoptysis	32 (12.2)
Shoulder, back, abdominal pain	8 (3.0)
Hoarseness	7 (2.7)
Loss appetite	6 (2.3)
Fatigue	4 (1.5)
Neck mass	2 (0.8)
Others (fever, headache, leg edema, orthopnea, syncope, face swelling)	8 (3.0)
Histology; n (%)	
Adenocarcinoma	199 (75.7)
Squamous cell carcinoma	31 (11.8)
Large cell carcinoma	2 (0.8)
Small cell carcinoma	11 (4.2)
Non-small cell carcinoma*	14 (5.3)
Combined small cell carcinoma	1 (0.4)
Carcinoid tumor	1 (0.4)
Neuroendocrine tumor	2 (0.8)
Poorly differentiated	2 (0.8)

SD=standard deviation

* There are no available specific subtype data

Discussion

Chest radiograph is widely known as not being an accurate screening tool for lung cancer even though it is used for screening in the high-risk lung cancer population[7]. The sensitivity of chest radiographs to detect lung cancer in symptomatic patients remains unclear.

Stephen et al[8], in a systematic review study, found that the sensitivity of chest radiographs in patients with symptomatic lung cancer was 77% to 80%. Normal and abnormal chest radiographs without suspicion of lung cancer were more than 20%. According to Stapley et al's study from primary care hospitals in England[9], up to 23% of lung cancer patients presenting with symptoms had a negative chest radiograph. In studies of patients with hemoptysis and normal chest radiographs, 6% to 21% were diagnosed with lung cancer after further testing using different methods[10-14].

Table 2. Chest radiograph results of patients with symptomatic lung cancer

Chest X-ray	n (%)	95% CI
Positive findings	229 (87.1)	84.4 to 90.9
Negative findings		
Abnormal: no cancer suspected	31 (11.8)	8.2 to 16.3
Normal	3 (1.1)	0.2 to 3.3

CI=confidence interval

Table 3. Chest radiograph findings and inter-reader agreement

Chest X-ray findings	n (%)
Abnormal: no cancer suspected	
Patchy infiltration	22 (8.4)
Reticular infiltration	2 (0.8)
Reticulonodular infiltration	3 (1.1)
Thin wall cavity	3 (1.1)
Other	1 (0.4)
Positive: cancer suspected	
Solitary pulmonary nodule	22 (8.4)
Pulmonary mass	126 (47.9)
Multiple pulmonary nodules	19 (7.2)
Golden S sign	3 (1.1)
Hilar mass	37 (14.1)
Apical pleural thickening	4 (1.5)
Widening mediastinum	2 (0.8)
Thick wall cavity	4 (1.5)
Pleural effusion	64 (24.3)
Lesion location	
RUL	66 (25.1)
RML	12 (4.6)
RLL	41 (15.6)
LUL	39 (14.8)
LLL	18 (6.8)
Hilar region	40 (15.2)
Retrocardiac region	1 (0.4)
Apical lung	7 (2.7)
Scattered	19 (7.2)
Mediastinum	2 (0.8)
Pleura	64 (24.3)
Size (cm); mean±SD	5.57±2.64

SD=standard deviation; RUL=right upper lobe; RML=right middle lobe; RLL=right lower lobe; LUL=left upper lobe; LLL=left lower lobe

In the present study, 12.9% of all patients with symptomatic lung cancer had negative chest radiograph. Tumor characteristics, size, conspicuity, tumor location, and tumor obscuration were major causes of negative findings in the present study.

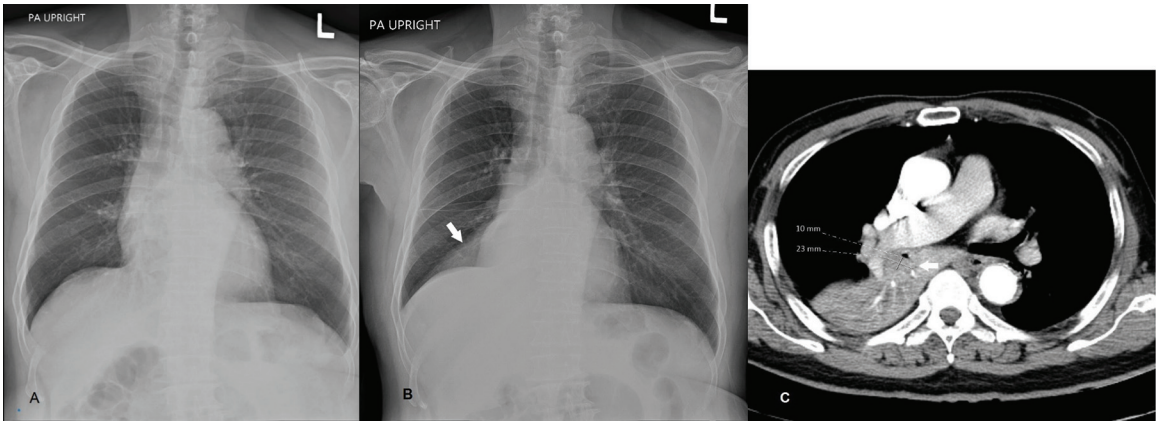

Figure 1. A 67-year-old man with intermittent cough for 1 year. (A) His first chest radiograph revealed normal even he experienced the symptom. (B) He developed non-massive hemoptysis 300 days after the first visit. His chest radiograph showed triangular shape opacity at the medial aspect of the right lower lobe with slightly decreased right lung volume. These findings could represent right lower lobe atelectasis, but there is no direct observation of any lung mass in this radiograph. (C) Further chest CT scan revealed an endobronchial mass in the right lower lobe bronchus, measuring about 10×23 mm, causing right lower lobe atelectasis. The tumor was confirmed to be a squamous cell carcinoma.

Tumor location, size, and conspicuity

Three patients from normal chest radiograph had a clinical presentation of cough (n=2) and hoarseness (n=1). Both cough patients developed non-massive hemoptysis and had abnormal chest radiographs during follow-up sessions at 300 days and 60 days after the first normal radiograph. CT findings revealed an endobronchial tumor in the intermediate and right lower lobe bronchus, as well as a 3.4-cm consolidation with a surrounding ground-glass appearance at the medial basal segment of the right lower lobe, respectively (Figure 1).

CT findings in the hoarseness patient revealed a 7.3-cm Pancoast tumor in the right apical lung. The present study patient also had a delay in performing CT scan because the serial follow-up chest radiograph had just revealed an abnormality at 120 days after the first visit (Figure 2).

These indicated that the detection of lung cancer on chest radiography depends on the location, size, and conspicuity of the tumor affect. An endobronchial mass without lung atelectasis was difficult to identify on a plain radiograph, even after symptoms were presented. Small tumor sizes located in hidden areas were also present. Even though this study aimed not to find a missed lung cancer, the causes of negative chest radiograph were likely the same as missed lung cancer. Two studies reported that the median diameter of a missed lesion was 16 mm[15,16]. The missed rate dropped in a larger tumor diameter[15]. These two studies also stated that unsharp tumor margin, affecting lesion conspicuity, was the majority of missed lesions in their studies[15,16].

Obscured primary tumor

The CT findings of patchy infiltration in the "abnormal, no cancer suspected group", were consolidation, as well as pulmonary mass, mass in the collapsed lung, and endobronchial mass with lung atelectasis.

Mass obscured in lung atelectasis or endobronchial mass causing lung atelectasis made it difficult to evaluate the primary tumor on plain radiograph. The two composite components of mass and atelectasis sometimes may not show significant lung volume loss on the radiograph. Findings could appear as airspace opacification. Additionally, patchy infiltration found in the first chest radiograph with uncertain symptom onset might remind us of acute airspace opacification causes, which are almost benign conditions[17,18], caused delay further investigation and management.

Two patients in the reticular and reticulonodular infiltration group had obscured lung cancer in pleural effusion with lung atelectasis and the other one was obscured by hilar shadow. The reticular and reticulonodular infiltration findings were multiple small pulmonary nodules on CT scan, which could be lung metastasis.

Pulmonary tuberculosis mimicking lung cancer

Pulmonary tuberculosis was the first diagnosis of one of the present study patients with reticulonodular

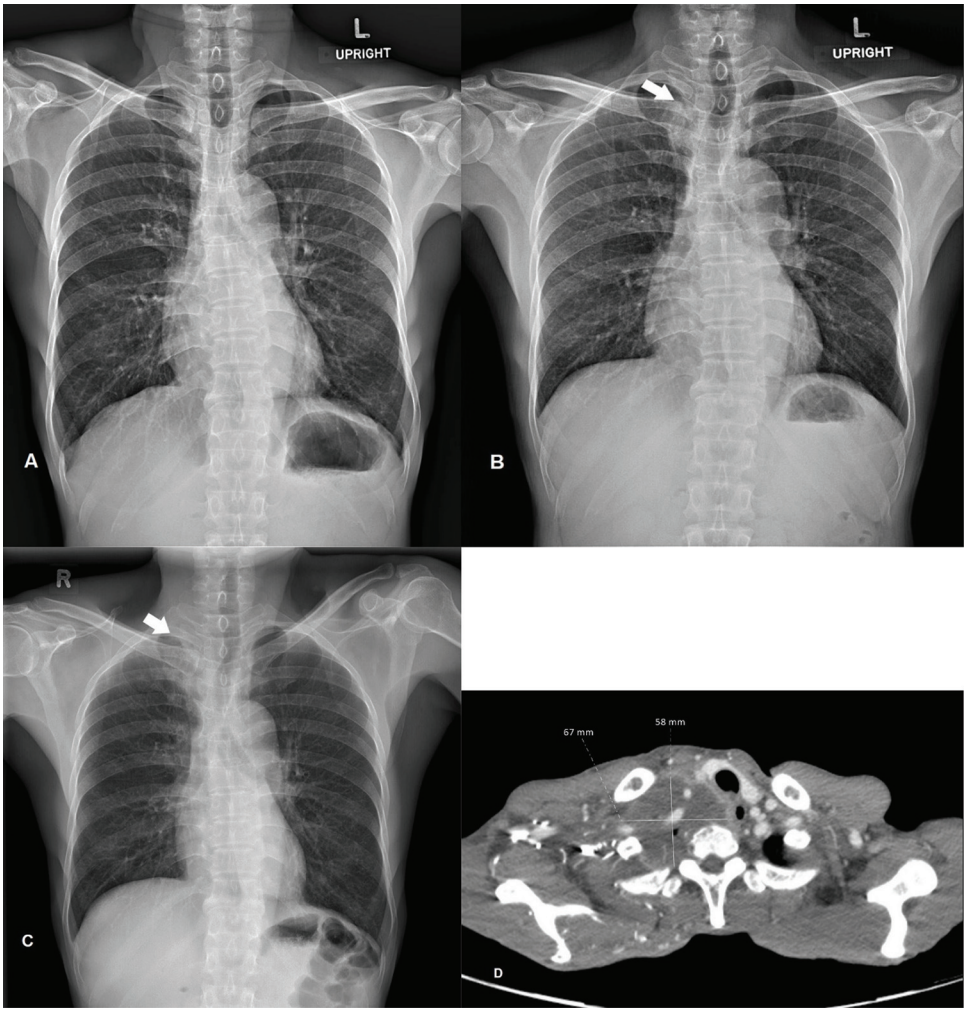

Figure 2. A 53-year-old man with hoarseness for 90 days. (A) His first chest radiograph was normal. (B) His followed up chest radiograph 39 days after the first visit revealed only a slightly prominent soft tissue at the right paratracheal stripe and mild tracheal shifted to the left side (white arrow). (C) His followed up chest radiograph at 120 days showed an increased size of a soft tissue lesion at the right paratracheal stripe and increased tracheal shifted to the left side (white arrow). (D) CT scan showed a Pancoast tumor at right apical lung, encasing the right common carotid artery and right subclavian artery and invading the superior venacava. The tumor size is about 5.8×6.7 cm.

infiltration in the right apical lung with suspicion of an enlarged right hilar lymph node on a chest radiograph. The primary tumor located in the right lower paratracheal area invaded the trachea and right main bronchus, causing mimic enlarged hilar lymph node on a plain radiograph (Figure 3).

Another patient from the "other findings group" had a history of pulmonary tuberculosis with complete treatment 20 years ago but presented with hemoptysis in the recent visit. Chest radiograph findings lead to diagnostic of pulmonary tuberculosis, seen as multiple calcified pulmonary nodules and non-calcified pulmonary nodules with fibrosis in both upper lungs. The largest nodule in the right upper lobe increased in size during follow-up and treatment of tuberculosis. Tissue diagnosis confirmed adenosquamous carcinoma at 410 days after the first visit.

The two patients from the present study were an excellent example of tuberculosis mimicking lung cancer. Mimicking of radiological features, similar symptoms, and how common both diseases in developing countries frequently caused misdiagnosis and delayed treatment[19-21]. Coexisting pulmonary tuberculosis is also challenging to distinguish cancer from tuberculosis lesions. Physicians and radiologists should always be aware of malignancy if patients had any risk of lung cancer.

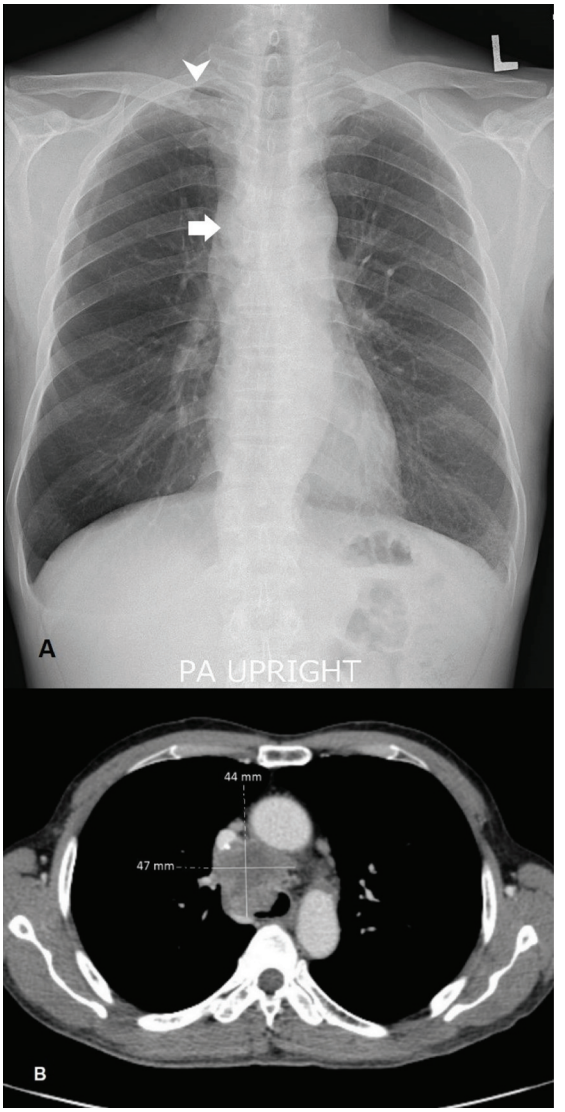

Figure 3. A 64-year-old man with non-massive hemoptysis for 60 days. (A) His first chest radiograph revealed reticulo-nodular infiltration at the right apical lung (white arrowhead) with suspicion of an enlarged right hilar lymph node (white arrow). (B) CT scan on the next day after the first visit showed an irregular border and heterogeneous enhancing mass at the right lower paratracheal area, invading the trachea and right main bronchus, causing mimic enlarged hilar lymph node on a plain radiograph.

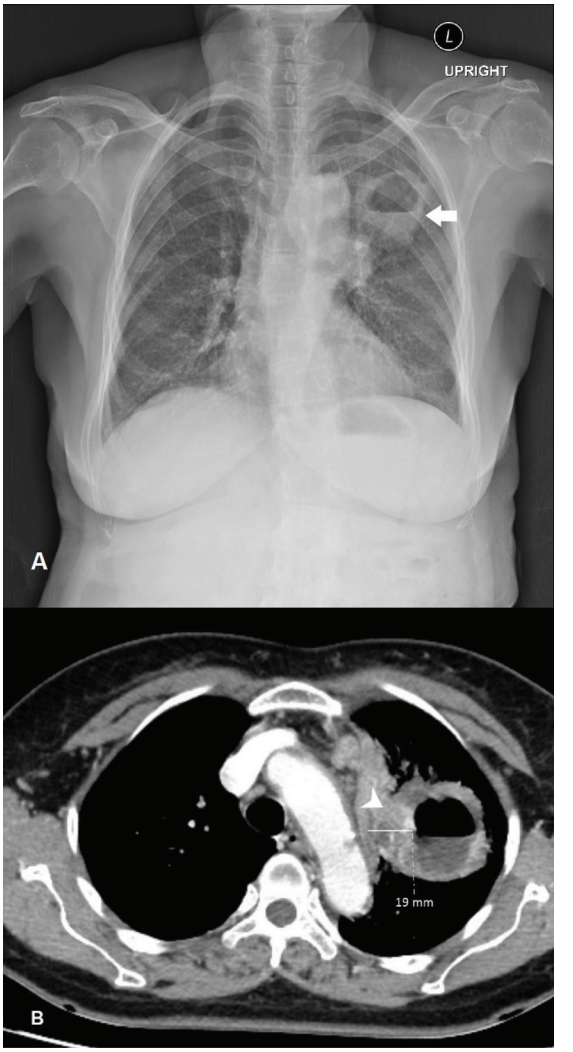

Figure 4. A 74-year-old woman with chronic cough for 21 days. (A) Her first chest radiograph revealed a cavity with the air-fluid level at LUL (white arrow). The visualized cavity wall measured about 9 mm in thickness, not meeting the threshold criteria for malignancy. An enlarged left hilar lymph node was also noted. (B) CT scan 39 days after the first visit showed an irregular and asymmetrical thickening wall cavity with fluid-filled at LUL. The maximal wall thickness was 19 mm, possibly obscured by the fluid on a plain radiograph (white arrowhead).

Lung cavity

The present study categorized two patients with lung cavities with gas-fluid levels and cavity wall thickness less than 16 mm on chest radiographs as benign findings. Previous studies[22-24] concluded that a cavity wall thickness less than 16 mm favored benign lesions. The gas-fluid level also rarely occurred in malignancy and is commonly caused by infection. Nevertheless, this conclusion is not always true, as there were reported evidence of thin wall malignant cavity series[25-27]. The measurement of cavity wall thickness was also inaccurate on a plain radiograph. One of the two patients had irregular and asymmetrical thickening cavity walls on CT scan (Figure 4). The thickest wall was obscured by fluid shadow on the chest radiograph. The other patient had an irregular wall with a spiculated border cavity at the left upper lobe whose wall thickness did not meet the threshold

thickness for malignancy.

Time interval until definite diagnosis

The average time interval from the first radiograph to definite diagnosis was significantly longer in the negative chest radiograph group, at 141.12 days in the negative findings group compared with 55.60 days in the positive findings group ($p<0.00001$). Foley et al also reported a longer time for further investigation and diagnosis in the negative chest radiograph subgroup[28]. Negative chest radiographs in symptomatic patients significantly caused delayed diagnosis and treatment.

The negative chest radiographs in the present study were lower than those in the previously reported studies[15,16]. Most of the patients in the present study had experienced the symptoms for a while before the doctor visit, and the symptom duration was 60 days with range of 1 to 1,095 days). The mean tumor size in the positive chest radiograph was 5.57±2.64 cm, which was a large and doubtlessly on chest radiograph.

Chest radiographs in the present study were sent from various primary and secondary healthcare centers. Various X-ray machines, techniques, and patient positions were used and caused limitations in the present study.

Conclusion

Negative chest radiographs can be found even in the presented lung cancer symptom patients, resulting in delayed diagnosis and treatment. Tumor characteristics, size, and location were the leading causes of negative imaging in the present study. Investigators using chest radiograph as a first-line imaging investigation, especially in high-risk lung cancer patients, should be mindful of false negatives. Considering shorter schedule for further CT scans would be beneficial in the negative chest radiograph symptomatic patient group.

What is already known prior to this study?

Chest radiograph is commonly used as first-line imaging investigation in patients with abnormal respiratory symptoms or any lung cancer symptoms. However, there were negative chest radiographs among patients with symptomatic lung cancer rated up to 23%.

What this study adds?

Negative chest radiograph in patients with symptomatic lung cancer was 12.9% in this study. Tumor location, size, conspicuity, obscured primary tumor, pulmonary tuberculosis mimicking lung cancer, and characteristic of lung cavity on radiograph were the leading causes of negative imaging. These negative chest radiographs caused further delayed in the investigation and treatment. Consider shortening the schedule for further CT scans would be beneficial in the negative chest radiograph symptomatic patient group, especially in high-risk lung cancer patients.

Conflicts of interest

The authors declare no conflict of interest.

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