Original Article

Etiology of size based pulmonary nodules in Asia.

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Abstract

OBJECTIVE: To determine whether the American College of Chest Physicians' lung nodule screening recommendation is an effective tool in diagnosing Asian patients with pulmonary nodules.

MATERIALS AND METHODS: This is a retrospective study of 36 patients from 2012-2014 that were identified to have had pulmonary nodules through chest CT scan results. The data collected from patients were evaluated then illustrated to find out the nature of lung nodules among Asian population. The pulmonary nodule is based on size alone regardless of other morphology for instance border, calcification etc.

RESULTS: Out of 36 patients, 23 were diagnosed with tuberculosis (TB), 19 tested positive for lung malignancy, 5 cases of TB co existing with cancer and 6 cases of non-tuberculous mycobacterium (NTM) infection. The types of lung cancer found were 7% small cell lung cancer, 7% squamous cell lung cancer and 86% adenocarcinoma. Nodule sizes were classified into 3 groups according to measurement. 4.5-11 mm (100% TB and 0% cancer), 12-20 mm (60% TB and 40% cancer) and 21-88 mm (52% TB and 48% cancer).

CONCLUSION: Lung nodule evaluation among Asian patients requires specific guidelines that consider the high prevalence of tuberculosis and other infections. The statistical results from our study proves that the American College of Chest Physicians' lung nodule screening recommendation, if practiced by Asian physicians, should be revised according to the current health status and presence of other diseases of the Asian population.

Keywords: CT scan, lung cancer, non-tuberculous myobacterium, pulmonary nodules, tuberculosis

A pulmonary nodule is a small, round-shaped opacity that maybe solitary or a multiple growth in the lungs.[1] These nodules found in chest x-ray or other radiographic images such as chest CT scan are generally more or less than 3 cms in diameter[2] which may be benign, caused by infection such as tuberculosis (TB) or malignancy.

Thailand is one of the 22 high TB-burden countries identified by World Health Organization (WHO). Various tests have been developed to screen and cure this disease. However, as the facilities and treatment become more accessible, this illness has evolved into worsening conditions such as multi-drug resistance, accompanying non-tuberculous mycobacteria infection and higher prevalence for immuno compromised patients. Lung cancer has remained as one of the leading causes of mortality in Thailand and worldwide.[3] A major reason behind this, is that pulmonary malignancy has high rates of being diagnosed in the late stages of the disease.[4] Several guidelines havebeen recommended and are being updated on how lung cancer screening should be implemented.[5] One of this is the use of low dose CT scan (LDCT) that has been recognized by the National Lung Cancer Screening Trial (NLST) todecrease mortality rate in high-risk population of lung cancer by 20%.[6]

Recent advances on CT scan imaging followed by further investigation techniques (if applicable) such as endobronchial ultrasound (EBUS), fiberoptic bronchoscopy (FOB), video assisted thoracoscopy (VATS), surgery and pathological diagnosis have played a key role in the early and accurate diagnosis

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of pulmonary nodules. The recent 3rd edition of the American College of Chest Physicians' lung nodule screening recommendation stated that evaluation begins in nodules measuring more or less 8 mm in diameter stressing the probability of malignancy and the benefits and harm of different approach strategies.

For several years, these guidelines have been a very useful pattern in determining the nature of pulmonary lung nodules. However, in Asia, several circumstances such as patient demographics have been a major factor in diagnosing lung nodules. Our goal is to evaluate whether the guidelines formulated in Western countries through the use of our extensive patient information collected in the past 2 years, should be used as a blueprint in finding out the cause of pulmonary nodules in Asia.

Materials and Methods

We retrospectively studied data of 36 patients from 2012-2014, who underwent chest CT scan and were identified to have pulmonary nodules. These patients underwent further investigation using EBUS, FOB, VATS or surgery to identify diagnosis. Demographic data collected were age, gender, smoking history (smoker or non-smoker), race (Asian or Caucasian expatriates) and nodule sizes. Specimens extracted from biopsy or surgery was evaluated by pathologist for infection or malignancy. The diagnoses were divided into two groups: infection (tuberculosis and NTM) or malignant. Polymerase chain reaction (PCR-TB) and AFB stain were done to identify tuberculosis. NTM was diagnosed when the PCR-TB result revealed presence of non-tuberculous mycobacteria (NTM). Cytopathology study was conducted to identify malignancy.

The diagnoses of the nodules were then divided into three groups according to their sizes. The first category has nodules measuring from 4.5-11 mm. The second group of nodules is 12-20 mm and the last group measures 21-88 mm. From these categories, the 36 patients were placed according to their final diagnoses and respective nodule sizes.

Results

Of the 36 patients, 12 were diagnosed with Tuberculosis, 9 tested positive for lung malignancy and 15 cases of tuberculosis co existing with cancer or NTM. Of the patients,41.6% were smokers and 58.3% were nonsmokers. The age range is from 22-87 years old (mean 49.1 ± 5.7). Table 1 shows clinical data of the 36 patients grouped based on final diagnosis.

The nodule sizes were classified into 3 groups. The first set measured 4.5-11 mm and100% tested positive for tuberculosis (TB) and no incidence of malignancy. The second group had a nodule size of 12- 20 mm. From this category, 60% were diagnosed with TB and 40% of these were malignant. The final classification of 21-88 mm nodule was identified to have 52% cases of tuberculosis and 48% of these were malignant.

The types of lung cancer found were small cell lung cancer (7%), squamous cell lung cancer (7%) and adeno-carcinoma (86%). There were 29 Asian and 7 Caucasian expatriates. Malignancy occurred in 38% of Asian patients and 71% in Caucasian expatriates. Tuberculosis was positive for 70% of Asians and only 57% of Caucasian expatriates.

Table 1: Demographic data classified according to diagnosis.

Clinical Features	Infection (TB or NTM) n(%)	Malignant n(%)
n	12	9
Age (Mean ± SD)	41 ± 16.3	55 ± 6.1
Gender		
Male	6 (50)	6 (66.6)
Female	6 (50)	3 (33.3)
Race		
Asian	10 (83.3)	7 (77.7)
Caucasian expatriates	2 (17)	2 (22.2)
Smoking history (n=36)		
Smokers	5 (41.6)	6 (66.6)
Non-smokers	7 (58.3)	3 (33.3)

The age bracket classified from 20-30 years old showed that 8% were diagnosed with TB. Those aged from 31-40 showed that 8% were diagnosed with TB, of which 6% were malignant, those aged from 41-50 showed that 16% were diagnosed with TB, of which 6% were malignant, those aged from 51-60 showed that 8% were diagnosed with TB, of which 53% were malignant, and those aged 61 and older showed that 60% were diagnosed with TB, of which 35% were malignant.

Table 2: Cytopathology results of pulmonary nodules according to size.

Nodule size (mm)	Infection (TB or NTM)	Malignancy
4.5 - 11	100%	0%
12 - 20	60%	40%
21 - 88	52%	48%

Discussion

When a patient is detected to have a pulmonary nodule in their chest radiograph or CT scan, the Clinician's critical responsibility is to mainly diagnose the nodule accurately so proper treatment can be prescribed. Establishing the correct diagnosis prohibits invasive procedures, unwanted treatments and avoids unnecessary anxiety and financial stress for the patient. Since the clinicians from some Asian countries do not have yet a standard protocol to follow that is based on the Asian population, most of the physicians utilize the American College of Chest Physicians (ACCP) Clinical Practice Guidelines in determining the nature of the lung nodule.

Using this guideline, patients presenting with solid nodules measuring > 8 mm should have their previous scans reviewed to determine any growth or changes. Then medical data and history such as age, smoking habits, family profile of lung cancer etc., should be collected to determine the probability of malignancy. Depending on the results of assessment and characteristic of nodule, the individual may proceed to undergo further diagnostic tests such as PET/CT scan, fiber optic bronchoscopy (FOB), endobronchial ultrasound (EBUS) and surgery to collect specimens for histopathology or may undergo the non-invasive route which is a series of chest CT scans.[7] These recommendations may have proven effective for patients in western medical settings but not for the Asian population where infection such as pulmonary tuberculosis is common in this region.[8]

Tuberculosis (TB) is a major global health problem particularly in developing countries. According to the 2014 report of the world health organization, there were an estimated 9.0 million incidences of TB worldwide, equivalent to 126 cases per 100,000 populations. The majority of cases in 2013 were recorded in Asia (56%) and the African Region (29%). Although the occurrence is decreasing gradually at 1.5% per year from 2000–2013 and 0.6% between 2012 and 2013, these numbers are still high compared to the western countries with TB estimated at only 4% from the European region and 3% in America.[9]

Diagnosis of TB is difficult in developing countries, especially in rural hospitals where there is lack of state of the art facilities and shortage of health care teams, well trained in handling this kind of infection. The common available methods used are sputum culture and sensitivity and chest x-ray.[10] In urban areas, diagnostic tests such as Quantiferon TB and CT scans are available to further study any nodule initially seen on chest x-ray. However, advanced technology is only being utilized by certain groups due to poor socioeconomic status and substandard health care systems causing delays in diagnosis of what could possibly be lung cancer.[11] TB exhibits radiological features and symptoms identical of pulmonary malignancy. In our study, nodules measuring 12-20 mms were found to be 60% TB and 40% malignant which shows that a nodule with such size could either be TB or cancer or TB coexisting with lung cancer. An attempt to accurately identify the cause of the nodule should be done by performing a lung biopsy, tissue analysis and blood tests to confirm diagnosis.

In a study conducted by Dr. Yu et al[7]., evidence has been found of the increased prevalence of lung cancer patients who were previously diagnosed with tuberculosis. In their research from 1998-2000, lung cancer prevalence was found to be 11-times higher in patients with tuberculosis, than patients who were never diagnosed with TB. Cox proportional hazard regression analysis showed that hazard ratio (HR) was 3·32 (95% CI 2·70 – 4·09) after adjustment for variables including chronic obstructive pulmonary disease (COPD) and other cancers aside from lung cancer related to smoking. The results were evident that tuberculosis may have intensified the possibility of having lung cancer. Another research in Yunnan province, China conducted by Engels et al, stated that their cohort study determined an increased risk of lung cancer following a diagnosis of TB among farmers in Xuanwei, China. The lung malignancy appeared greatest within the first five years after TB diagnosis. Also, the risk for lung cancer remained three-fold increased for more than ten years after TB diagnosis.[12] In our study 67% of cases were diagnosed with TB and in Thailand, there were 66,415 TB cases in 2013 reported by WHO.[7] To our knowledge, there have been no reports of lung cancer patients who were previously diagnosed with tuberculosis in Thailand.

From the 1950s-1980s, the mortality rate of women from lung cancer has increased from 0.9 to 8.5 per 100,000 population in Taiwan, 3 to 11.5 in Japan and 11.4 to 28.5 in Hong Kong.[13,14] In our previous study, we found that

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the occurrence of lung cancer in female passive smokers were significantly high at 17.7% among 226 patients and adenocarcinoma as the most common type of cancer in this group accounting for 41.6%.[15] Adenocarcinoma became the major type of cancer for non-smoking Asian women. In the 1990s-2000s, 52-65% was recorded to be diagnosed with this type of lung malignancy.[13] In our research, 86% were diagnosed with adenocarcinoma, proving that this type of cancer has become a predominant type of lung malignancy among Asian patients. Smoking has been known as the leading cause of lung cancer for both genders. In the US, 10% of patients diagnosed with lung cancer have never been smokers while in Asia, 30% of patients diagnosed with lung malignancy are non-smokers and more than half are female.[16] This conveys that although smoking is the major reason for the incidence of lung cancer in Asian males, several factors should be considered as the causative factors for Asian females diagnosed with cancer.

A number of known aspects different from western countries have also been identified as contributors to lung cancer among Asian women. In China, 17% of lung cancer in females is due to indoor pollution caused by coal burning.[17] The exposure to cooking oil fumes,[13] family history and genetic makeup all contributes to the development of lung cancer.[13,18] Aside from tuberculosis, other infections such as Microsporum canis infection in northern Thai women, has also been involved in the etiology of female lung cancer.[19]

A study conducted by Swensen et al,[20] presented some similar findings on the percentage of malignancy of lung nodules based on its size. In our study, pulmonary nodules measuring > 21 mm had a 48% rate of malignancy. On the other hand, Swensen's study presented 75% of their cases were malignant as shown in Table 2. In our research, pathology reports revealed 86% are adenocarcinoma, while 42% were found in Swensen's study.[20, 21] Although several factors have been discussed on the differences between Western and Asian population in lung nodule evaluation, this particular study however, presented that lung nodule size is a major factor in order to diagnose lung cancer.

Table 3: A study reported by Swensen et al. on the relationship between the size of lung nodules and the chance of malignancy.

Nodule Size (mm)	Total	Malignancy
< 4	2038	0%
4 - 7	1034	1%
8 - 20	268	15%
> 20	16	75%

To summarize, the presence of pulmonary nodules in radiographic examinations among Asian patients may have several causes aside from being malignant and benign. This could be tuberculosis, non-tuberculous mycobacteria infection, bronchitis caused by fungi infection and other diseases that mimic the signs and symptoms of lung cancer. This study suggests that although solid nodules measuring < 8 mm are infrequently malignant, further tests such as tissue analysis should be done to rule out not just malignancy but also other infections that in the long run, may also have contributed to the development of lung cancer. Chest x-ray or CT scan monitoring of a nodule, without ruling out other diseases may not be conclusive enough in handling pulmonary nodules among the Asian population.

Conclusion

Pulmonary nodule evaluation is a complex study that requires specific guidelines for certain populations. Although there have been numerous recommendations from several recognized organizations, we believe that the statistical results in Asia do not apply to the current guidelines being followed which is to further evaluate nodules with the size of more or less than 8 mm. People living in Asia, still have a high prevalence of tuberculosis unlike those seen in western countries which should be highly considered in identifying the etiology of lung nodules in Asia. Therefore, formulating a particular and different guideline for the evaluation of lung nodules that is more appropriate for high-TB burden countries is highly recommended.

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