Early detection of central airway lung cancer in smokers with silicosis

A. I. L. Lo,*† Y. Huang,†‡ S. Y. Lam,§ A. H. K. Cheung,† R. Au,§ C. C. Leung,§ W. K. Lam,† M. S. M. Ip,† M. Chan-Yeung,† B. Lam†

*Department of Respiratory Medicine, Centro Hospitalar Conde de São Januário, Macao SAR; †Department of Medicine, University of Hong Kong, Hong Kong SAR; ‡Department of Respiratory Medicine, Daping Hospital, Third Military Medical University, Chong Qing, Sichuan; §Department of Health, Hong Kong SAR, China

Correspondence to: Lam Bing, Respiratory Medicine Centre, Hong Kong Sanatorium and Hospital, 2 Village Road, Happy Valley, Hong Kong SAR, China. Tel: (+852) 2835 8673. Fax: (+852) 2892 7513. e-mail: binglam@hksh.com


BACKGROUND: Smokers with silicosis are at increased risk of lung cancer.

OBJECTIVE: To evaluate the feasibility of using autofluorescence bronchoscopy after sputum examination for early detection of large airway lung cancer and factors associated with the presence of cancerous and precancerous lesions among smokers with silicosis.

METHODS: Subjects at the pneumoconiosis clinic were recruited if they fulfilled the following criteria: 1) age ≥40 years, 2) smoking history of ≥20 pack-years and 3) confirmed diagnosis of silicosis. Sputum specimens were collected for cytology/cytometry examination and autofluorescence bronchoscopy was performed in subjects with an abnormal sputum result.

RESULTS: A total of 48 subjects were recruited during the study period. The mean age and smoking history were respectively 63 ± 10 years and 51 ± 30 pack-years. Intraepithelial lung cancers and pre-neoplastic lesions (squamous metaplasia or above) were detected in respectively 2 (4.2%) and 14 (29.2%) subjects. The proportions of current smokers (75.0% vs. 40.6%, \( P = 0.03 \)) and asbestos exposure (37.5% vs. 9.4%, \( P = 0.04 \)) were significantly higher in subjects with the above lesions compared with those without.

CONCLUSIONS: Sputum examination followed by autofluorescence bronchoscopy may be a useful way of identifying cancerous/pre-cancerous lesions among silicotic smokers. Current smoking and asbestos exposure were associated with these lesions.

KEY WORDS: lung cancer; silicosis; autofluorescence bronchoscopy; early detection

SUMMARY

LUNG CANCER is the leading cause of cancer-related deaths, with a dismal 5-year survival of less than 15%. The prognosis of lung cancer patients is closely related to tumour size and stage of disease. More than 90% of patients with early central airway cancer survived at 5 years with either surgical or bronchoscopic treatment.

Smokers with silicosis are at increased risk of developing lung cancer. However, the background radiological abnormalities of silicosis make radiological detection of lung cancer difficult. Sputum cytology examination is sensitive in detecting central airway lung cancers. It has been shown that the presence of moderate atypia or worse in sputum may predict squamous cell carcinoma in individuals at high risk for lung cancer.

Autofluorescence bronchoscopy, which utilises the spectral difference in fluorescence and absorption properties between normal and abnormal bronchial epithelium, is several times more sensitive in detecting pre-neoplastic lesions and intraepithelial lung cancers than conventional white-light bronchoscopy (WLB). While some studies have shown that sputum cytology examination followed by autofluorescence bronchoscopy is a practical way of identifying early central lung cancers among smokers, others have failed to prove its superiority in detecting precancerous lesions over WLB. The discrepancy may be due to the population screened. To date, no studies have been performed on the role of this early detection tool in detecting precancerous and early cancerous lesions among patients with silicosis in whom radiological screening is not appropriate. The use of autofluorescence bronchoscopy may also help to delineate factors associated with the presence of these subtle endobronchial lesions.

The purpose of the present study was to evaluate the feasibility of using autofluorescence bronchoscopy...
after sputum examination as a tool for early detection of large airway lung cancer and factors associated with the presence of cancerous and pre-cancerous lesions among smokers with silicosis.

MATERIALS AND METHODS

Study subjects
From June 2006 to March 2009, all patients followed up at the designated Pneumoconiosis Clinic of Hong Kong were invited to join the study if they fulfilled the following inclusion criteria: 1) age ≥ 40 years; 2) smoking history of ≥ 20 pack-years; and 3) confirmed diagnosis of silicosis. The diagnosis of silicosis was based on significant occupational exposure to silica-containing dust and radiographic changes consistent with silicosis, with or without histological proof. A ‘confirmed’ case of silicosis was determined by the Pneumoconiosis Medical Board, an official committee for pneumoconiosis compensation assessment in Hong Kong.

Demographic and clinical characteristics, occupational exposure, smoking history, profusion score of pneumoconiotic nodules and the size of progressive massive fibrosis (PMF) were documented. An ex-smoker was defined as a smoker who had quit for ≥ 1 year; all other smokers were regarded as current.

Sputum examination
From June 2006 to August 2008, subjects were asked to provide early morning sputum for 3 consecutive days. All fresh specimens were examined by trained cytotechnologists under the supervision of a pathologist (SYL) in the Cytology Laboratory of the Department of Health. The results were reported as unsatisfactory, normal, atypia, suspicious for cancer and cancer. From September 2008 to March 2009, sputum samples were collected through sputum induction using Lung Flute (Medical Acoustics, Buffalo, NY, USA), which is particularly useful for patients unable to produce sputum spontaneously. In addition to the cytology examination, all sputum samples were sent for cytometry examination using an automated high-resolution image cytometer (LungSign™, Perceptronix Medical Inc Laboratories, Vancouver, BC, Canada). Both lung cancer likelihood-related LungSign score and DNA ploidy index were reported.

Subjects with a cytology report of sputum atypia or above or a sputum cytometry report of indeterminate or increased likelihood of malignancy or abnormal DNA index were invited to undergo bronchoscopy and spirometry at the Queen Mary Hospital, the main teaching hospital of the University of Hong Kong.

Bronchoscopy
Bronchoscopic examination was performed under local anaesthesia in the endoscopy suite by a bronchoscopist (BL) who was experienced in performing autofluorescence bronchoscopy. Conventional WLB was performed first, followed by autofluorescence bronchoscopy (SAFE-1000 System of Autofluorescence Endoscopy, Pentax, Asahi Optical, Tokyo, Japan, or Autofluorescence Imaging, Olympus, Tokyo, Japan). Both systems have been demonstrated to have a sensitivity of ≥ 90% in the detection of precancerous lesions and carcinoma in situ (CIS) by previous clinical studies. All abnormal sites detected by WLB, autofluorescence bronchoscopy or both were videotaped, recorded and biopsied. The location of each biopsy in the bronchial tree was precisely recorded using the international bronchial location classification. All biopsy specimens were examined by qualified pathologists and classified according to the World Health Organization classification into normal; hyperplasia; metaplasia; mild, moderate, or severe grade dysplasia; CIS; and invasive carcinoma.

Spirometry
Standard spirometry was performed before bronchoscopy by qualified technicians using Vmax (Viasys SensorMedics, Yorba Linda, CA, USA). Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured and expressed as a percentage of the predicted value based on a prediction equation for the Chinese population. Airflow limitation was defined as a ratio of FEV1 to FVC of < 70%.

Management
Patients with invasive lung cancer were managed according to the current standard of care. Subjects with intraepithelial lung cancer (severe dysplasia and CIS) were treated with endobronchial cryotherapy (ERBE Elektromedizin GmbH, Tübingen, Germany) and reassessed periodically with WLB and autofluorescence bronchoscopy at 3, 6, 12 and 24 months. Subjects with pre-neoplastic lesions (squamous metaplasia and dysplasia) were followed up with WLB and autofluorescence bronchoscopy every 6 months until the lesions regressed. All abnormal sites detected and sites that had received treatment were biopsied at re-assessment. We gave general physician’s advice for smoking cessation to all participants in the study.

Outcome
The outcome of this cohort, including the number of patients with lung cancer and the stage distribution, was determined from patient records reviewed in July 2009.

Ethical considerations
Ethical approval was obtained from the institutional review board of both the Department of Health and the University of Hong Kong. Informed consent was obtained from each subject.
Subjects were divided into two groups for analyses: Group 1 included patients with endobronchial biopsy revealing squamous metaplasia or above, and Group 2 those without endobronchial lesion or biopsy showing hyperplasia or below. Continuous data were expressed as mean ± standard deviation (SD) and categorical data were presented as percentage. The Fisher’s exact test and the two independent sample t-tests were used to compare dichotomous and continuous data between the two groups. *P* < 0.05 was considered statistically significant. SPSS 15.0 for Windows (Statistical Package for Social Sciences, Chicago, IL, USA) was used for all statistical analyses.

**RESULTS**

**Demographic characteristics**

From June 2006 to March 2009, we screened 720 subjects with silicosis. A final total of 48 eligible Chinese male subjects with sputum abnormalities were recruited into the study. The mean age of this cohort was 63 ± 10 years (range 48–82), with an accumulated smoking history of 51 ± 30 pack-years. The demographic data, occupational exposure, spirometric results and type of sputum abnormality are shown in Table 1.

**Sputum abnormality, bronchoscopy and lung cancer**

Among the 48 subjects with sputum abnormality, 37 (77.1%) had sputum atypia and 11 (22.9%) had abnormal cytometry (Table 1).

Endobronchial lesions were detected in 30 (62.5%) subjects and a total of 69 biopsies were performed: 12 (17.4%) were in the right upper lobe, 8 (11.6%) in the right middle lobe, 18 (26.1%) in the right lower lobe, 12 (17.4%) were in the right upper lobe, 8 (11.6%) in the left upper lobe, 6 (9.4%) in the left middle lobe, 1 (1.4%) in the left lower lobe, 1 (1.4%) in the left main bronchus, and 1 (1.4%) in the carina. Among the 69 biopsies performed, 17 (24.6%) were found to be squamous metaplasia or above.

Of the 48 subjects recruited, 2 (4.2%) were found to have intraepithelial neoplasm (CIS or severe dysplasia), 4 (8.4%) had mild to moderate dysplasia, 10 (20.8%) had squamous metaplasia and 14 (29.2%) showed either inflammation or normal epithelium.

There were no significant differences in the proportions of subjects harbouring squamous metaplasia or worse between subjects with abnormal sputum cytology and those with cytometry abnormality (32.4% vs. 36.4%, *P* = 0.81) and between subjects providing early morning sputum and those providing induced sputum (34.3% vs. 30.8%, *P* = 0.82).

Compared to subjects with normal bronchoscopical findings or biopsy showing hyperplasia or below, the proportion of current smokers (75.0% vs. 40.6%, *P* = 0.03) and exposure to asbestos (37.5% vs. 9.4%, *P* = 0.04) were significantly higher in those harbouring epithelial metaplasia or above. There was no statistically significant difference in chest symptoms, comorbidities, spirometric results, profusion score and PMF size between the two groups (Table 2).

**Outcome**

With a median follow-up of 23.8 months, no other lung cancer cases were diagnosed in this cohort other than the two detected by screening. For the two with

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**Table 1** Characteristics and type of sputum abnormality in 48 male subjects with silicosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%) or mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [range]</td>
<td>63 ± 10 (48–82)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>51 ± 30</td>
</tr>
<tr>
<td>Exposure to asbestos</td>
<td>9 (18.8)</td>
</tr>
<tr>
<td>Spirometric result</td>
<td></td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>81 ± 22</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>98 ± 16</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Airflow limitation</td>
<td>32 (66.7)</td>
</tr>
<tr>
<td>Sputum cytology abnormality</td>
<td></td>
</tr>
<tr>
<td>Atypical cells</td>
<td>37 (77.1)</td>
</tr>
<tr>
<td>Sputum cytometry abnormality</td>
<td></td>
</tr>
<tr>
<td>High LungSign score</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>Indeterminate LungSign score</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>Abnormal DNA index</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>

SD = standard deviation; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity.

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**Table 2** Clinical characteristics of patients with endobronchial biopsy revealing squamous metaplasia or above, and patients with normal to hyperplasia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Squamous metaplasia or above (n = 16)</th>
<th>Normal to hyperplasia (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62.3 ± 11.6</td>
<td>64.1 ± 9.7</td>
</tr>
<tr>
<td>Old tuberculosis</td>
<td>3 (18.8)</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>1 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12 (75.0)</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>54.7 ± 42.4</td>
<td>49.2 ± 22.3</td>
</tr>
<tr>
<td>Exposure to asbestos</td>
<td>6 (37.5)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Profusion score</td>
<td>1 (including 0/1, 1/0, 1/1) 9 (56.3)</td>
<td>20 (62.5)</td>
</tr>
<tr>
<td>2 (including 1/2, 2/1, 2/2) 7 (43.8)</td>
<td></td>
<td>10 (31.3)</td>
</tr>
<tr>
<td>3 (including 2/3, 3/2, 3/3) 0</td>
<td></td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>PMF size</td>
<td>14 (87.5)</td>
<td>24 (75.0)</td>
</tr>
<tr>
<td>A to C</td>
<td>2 (12.5)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>77.9 ± 23.4</td>
<td>82.1 ± 21.1</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>97.6 ± 16.7</td>
<td>97.6 ± 15.6</td>
</tr>
<tr>
<td>FEV1/FVC ratio, %</td>
<td>61.8 ± 13.9</td>
<td>64.1 ± 11.7</td>
</tr>
<tr>
<td>Airflow limitation*</td>
<td>11 (68.8)</td>
<td>21 (65.6)</td>
</tr>
</tbody>
</table>

* Defined as a FEV1 to FVC ratio of < 70%.

SD = standard deviation; PMF = progressive massive fibrosis; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
intraepithelial neoplasm, the surveillance time was respectively 35.8 and 8.2 months.

DISCUSSION

It is generally accepted that squamous cell carcinoma develops in a gradual and stepwise fashion from normal epithelium, to hyperplasia, squamous metaplasia, dysplasia, and towards CIS and invasive carcinoma.20 If the pre-cancerous and pre-invasive lesions can be detected and treated, the development of lung cancer may be arrested.

By using a combination of sputum cytology/cytometry and autofluorescence bronchoscopy as a screening tool, we found that 4.2% of the silicotic patients with sputum abnormality had intraepithelial (Stage 0) lung cancer. Previous research has shown that the progression rates from severe dysplasia to CIS/invasive cancer and from CIS to invasive cancer were respectively 32% and 21% over 4 to 17 months.21 If no intervention was performed, respectively a third and more than half of the patients harbouring these lesions would develop invasive lung cancer at 1 and 2 years.24 In our two subjects with intraepithelial neoplasm who received endobronchial cryotherapy, no tumour progression was observed during the follow-up period. For those subjects without intraepithelial neoplasm, no malignancy was detected with a median follow-up of nearly 2 years.

In our cohort, squamous metaplasia and mild to moderate dysplasia were detected in 29.2% of the subjects. Although squamous metaplasia is sometimes regarded as a benign and reversible process, up to 9% of patients progress to intraepithelial lung cancer with a median follow-up of 21 months.23 The progression rate is similar to that of mild to moderate dysplasia.25 Subjects harbouring these lesions should also therefore be followed up regularly.

Pre-cancerous or cancerous lesions were identified in a third of our patients. Current smoking and a history of asbestos exposure were associated with an increased risk of such lesions. Our findings suggest that autofluorescence bronchoscopy is essential for silicotic patients presenting with sputum abnormalities, particularly in the case of current smokers or those with a history of exposure to asbestos.

In our cohort, the positive yields of autofluorescence bronchoscopy were similar in patients undergoing sputum cytology and those with cytometry as the initial test. Given its low cost and wide availability, conventional sputum cytology remained a good choice for initial lung cancer screening among smokers with silicosis. Previous studies have demonstrated that automated sputum DNA cytometry had comparable efficacy in detecting central airway lung cancer to that of conventional sputum cytology.17,24 Our study findings further confirm that sputum DNA abnormality detected by automated cytometry should be investigated in the same way as sputum atypia, and that bronchoscopic examination with AFB, if available, is a good option.

Our study had several limitations. First, peripherally located lung cancers, especially adenocarcinoma, may have been missed in our cohort as computed tomography (CT) of the thorax was not used. However, our target population consisted of silicotic males with a smoking history in whom the relative risk for squamous cell carcinoma was much higher than that of adenocarcinoma. It is therefore reasonable to assume that few peripheral lung cancers, which were not our screening target, would be missed. In addition, CT thorax might be inappropriate for lung cancer detection in silicotic patients due to the background radiological abnormalities.6 Second, we have no follow-up data for those who were screened but who could not be recruited into the study due to limited resources. Third, this pilot study involved only a small number of subjects, and the conclusions of the study need to be verified in a larger cohort.

Acknowledgement

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References


CADRE : Le risque de cancer du poumon est augmenté chez les fumeurs atteints de silicose.

OBJECTIF : Évaluer la faisabilité d’utiliser la bronchosкопie avec autofluorescence après examen des crachats pour la détection précoce des cancers des grandes voies aériennes et évaluer les facteurs associés avec la présence de lésions cancéreuses et précancéreuses chez les fumeurs atteints de silicose.

MÉTHODES : On a recruté les sujets à la Clinique de la Pneumoconiose lorsqu’ils répondaient aux critères suivants : 1) âge ≥40 ans, 2) antécédents de ≥20 années-paquet de tabagisme, et 3) diagnostic confirmé de silicose. On a prélevé les échantillons de crachats pour examens cytologique et cytométrique et on a recouru à la bronchoscopie avec autofluorescence chez les sujets dont le résultat des crachats était anormal.

RÉSULTATS : Au cours de la période d’étude, on a recruté 48 sujets. L’âge moyen et les antécédents de tabagisme étaient respectivement de 63 ± 10 ans et de 51 ± 30 années-paquet. Les cancers pulmonaires intraépithéliaux et les lésions précancéreuses (méetaplasies pavimenteuses ou davantage) ont été détectés respectivement chez 2 (4,2%) et 14 (29,2%) des sujets. Chez les sujets présentant ces lésions par comparaison avec ceux n’en ayant pas, la proportion des fumeurs actuels était significativement plus élevée (75,0% vs. 40,6%; P = 0,03), de même que l’exposition à l’amiante (37,5% vs. 9,4%; P = 0,04).

CONCLUSIONS : L’examen des crachats suivi d’une bronchoscopie avec autofluorescence pourrait être une manière utile d’identifier des lésions cancéreuses/précancéreuses chez les fumeurs silicotiques. Ces lésions sont en association avec le fait de fumer actuellement et avec l’exposition à l’amiante.

RÉSUMÉ

MARCO DE REFERENCIAS : Los fumadores que padecen silicosis presentan un riesgo aumentado de cáncer de pulmón.

OBJETIVO: Evaluar la factibilidad de practicar la broncoscopia fluorescente después del examen del esputo, con el fin de detectar en forma temprana la presencia de lesiones cancerosas y precancerosas en los fumadores que sufren de silicosis.

MÉTODOS: Se incluyeron en el estudio pacientes de la consulta de neumoconiosis cuando cumplían con los siguientes criterios: 1) tener ≥40 años de edad; 2) presentar antecedentes de tabaquismo ≥20 paquetes-año; y 3) tener un diagnóstico confirmado de silicosis. Se recogieran muestras de esputo para examen citológico y en los pacientes con resultados anormales en la muestra de esputo citométrico y se practicaría la broncoscopia fluorescente.

RESULTADOS: Se incluyeron 48 pacientes durante el período del estudio. La media de la edad fue 63 ± 10 años y del tabaquismo 51 ± 30 paquetes-año. Se detectaron lesiones de cáncer intraepitelial del pulmón en dos personas (4,2%) y lesiones precancerosas (metaplasia escamosa o más avanzadas) en 14 (29,2%). La proporción de fumadores actuales (75,0% contra 40,6%; P = 0,03) y de exposición al amianto (37,5% contra 9,4%; P = 0,04) fue significativamente mayor en las personas que albergaban las lesiones precancerosas, en comparación con las personas que no las presentaban.

CONCLUSIÓN: El examen del esputo seguido de broncoscopia fluorescente podría ser una estrategia eficaz de detección de las lesiones cancerosas y precancerosas en los fumadores silicóticos. El tabaquismo actual y la exposición al amianto se asociaron con la presencia de estos tipos de lesiones.