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ORIGINAL ARTICLE

RISK OF LUNG CANCER IN PATIENTS WITH PREINVASIVE BRONCHIAL LESIONS FOLLOWED BY AUTOFLUORESCENCE BRONCHOSCOPY AND CHEST COMPUTED TOMOGRAPHY

By

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To assess risk of lung cancer (LC) in patients with preinvasive bronchial lesions and to identify factors associated with higher risk, 124 patients with one or more preinvasive bronchial lesions and normal chest computed tomography (CT) (mean age 66.7 years, 121 males and 3 females), followed-up by white light and autofluorescence bronchoscopy (AFB) every 4-6 mo and chest CT every 6-12 mo, end points were development of carcinoma in situ (CIS) or LC. Among 124 patients with 240 preinvasive bronchial lesions, 20 CIS or LC lesions were detected during follow-up in 20 (16%) patients, 7 were detected as new endobronchial lesions, 10 as new peripheral lesions and 3 as local progression from severe dysplasia to CIS. Median time to progression was 24 months (range: 6-54 mo). The Cumulative risk of progression was 7% at one year, 20% at three years and 44% at 5 years. Among detected lung cancers, 80% were stage 0 or stage I and underwent treatment with curative intent. Diagnosis of new SD during follow-up (p=0.0001), chronic obstructive pulmonary disease (COPD) (p = 0.001) or smoking index >52 packyear (p = 0.042) was associated with higher risk. Even after controlling for other risk factors,COPD was associated with risk of progression. Baseline lesion grade was not predictive of patient outcome (p = 0.146).Patients with preinvasive bronchial lesions, especially those with new SD during follow-up, COPD or smoking >52 pack-year are at high risk of LC, AFB and CT follow-up facilitated early detection and treatment with curative intent.

Keywords: *Lung cancer, Autofluorescence bronchoscopy, preinvasive bronchial lesion,squamous dysplasia, early detection.*

Abbreviations: ***AFB= Autofluorescence Bronchoscopy, WLB= White light bronchoscopy, CT= Computed Tomography, COPD= Chronic Obstructive Pulmonary Disease, LC= Lung Cancer, CIS= Carcinoma in situ, BCH= Basal Cell Hyperplasia, SM= Squamous Metaplasia, SD= Squamous Dysplasia.***

INTRODUCTION

Thoracic oncology providers confronted with the task of diagnosing and following patients at risk for cancer of the lung face a number of major dilemmas. First, the majority of patients with lung cancer (LC) are diagnosed at a late stage and, 15% survive 5 years. Second, risk paradigms are changing, from smoking only to occupational, environmental or home carcinogens to the risk associated

with premalignant airway changes. Third, advances in early diagnostic options have the potential to discover lung carcinoma while still in a preinvasive stage, minimally invasive stage or as small peripheral nodules.[1]

The proposed progression model for bronchial squamous cell carcinoma, from premalignant lesions to invasive cancer, includes the sequential development of basal cell hyperplasia (BCH), squamous metaplasia, mild, moderate and severe dysplasia, carcinoma in situ (CIS) and finally invasive LC.[2] White light bronchoscopy (WLB) is limited in its ability to detect small intraepithelial and microinvasive bronchial lesions, which may be only a few cells thick and might only have a surface diameter of a few millimeters. Autofluorescence bronchoscopy (AFB) was developed to address this limitation by WLB; AFB is now an established technique that has proven to be a far more sensitive method for detecting preinvasive and microinvasive bronchial lesions than WLB.[3-10] Kennedy et al, after reviewing several publications regarding the natural course of preinvasive bronchial lesions, reported that the observed rates of progression to invasive carcinoma ranged from 0% to 9% for moderate dysplasias and from 0% to 32% for severe dysplasias. CIS lesions either persist in > 60% cases with no regression or progress to invasive carcinoma in 20% to 60% of cases.[11]

The entire bronchial epithelium is exposed to carcinogens from cigarette smoke, and malignancy can develop at any location within the exposed epithelium.[12] In addition, there is a discrepancy between the prevalence of preinvasive lesions and the incidence of lung cancer, which suggests that not all lesions inevitably develop into carcinoma.[13,14] It is also reported that patients with preinvasive bronchial lesions can develop carcinoma at a remote site rather than the follow-up site.[15]

Taken together, an understanding of the natural history of preinvasive bronchial lesions and risk of lung cancer in patients harboring these lesions is central to both the management and follow-up of manifest lesions. This study was conducted to assess risk of LC in patients with bronchial preinvasive lesions and to identify factors associated with higher risk.

PATIENTS AND METHOD

Patients: From 335 consecutive patients at risk of LC who underwent AFB examination at Chiba University Hospital, Chiba, Japan during the period December 1999 to December 2008,124 patients were included in this study. At baseline, these patients had one or more preinvasive bronchial lesions, baseline chest computed tomography (CT) non-suspicious for LC and they had at least a 4 mo follow-up. Patients excluded from study included 126 with baseline CIS and/or more invasive lesion, 60 with no preinvasive lesions both at baseline and after 6 mo, and 25 with preinvasive lesions but without follow-up (refused second bronchoscopy and continued followup by sputum cytology). Our study included 121 males and 3 females, mean age 66.7 years (range: 44-84 yrs.), 105 with abnormal sputum cytology and 19 with past aerodigestive cancer.

Patient baseline clinical characteristics, including smoking history, are shown in Table 1.

Patients with severe dysplasia were considered a high grade group, and those with mild or moderate dysplasia were grouped as low grade. Patients were considered to have chronic obstructive pulmonary disease (COPD) if their post-bronchodilator FEV1/FVC ratio was <70%.[16] All participants provided written informed consent before enrollment into the study. Ethical approval was granted by the Chiba University ethics committee.

Table 1. Patient baseline demographic and clinical characteristics.

Total number of individuals	**124**
Gender	**121 (97.6%)**
Male	
Female	**3 (2.4%)**
Age mean (range) years	**66.7 (44-84)**
Smoking history	
Current smokers	**90 (72.6%)**
Ex-smokers	**29 (23.4%)**
Non-smokers	**5 (4%)**
Medical History	
Abnormal sputum cytology	**105 (84.7%)**
At risk of subsequent primary	**19 (15.3%)**
Past lung cancer	**15**
Past other aerodigestive cancer	**4**

Endoscopy: White light bronchoscopy (WLB) done using flexible video bronchoscope (BF-240, Olympus Optical Corporation, Tokyo, Japan from December 1999 until January 2004, and by BF 6C260, Olympus Optical Corporation, Tokyo, Japan thereafter). WLB was first performed under local anesthesia with sedation by intravenous midazolam and oxygen inhalation. This was followed by Autofluorescence bronchoscopy (AFB) using Laser Induced fluorescent endoscopy (LIFE) (Xillix LIFE; Xillix Technologies Corp., Richmond, BC, Canada) which was applied using a fiberoptic bronchoscope (BF40; Olympus) from December 1999 to October 2001, or by autofluorescence imaging (AFI) bronchovideoscope (BF type F260, Olympus Optical Corporation, Tokyo, Japan)

thereafter. Biopsy was taken from all sites that appeared abnormal at baseline and/or follow-up white light and/or autofluorescence bronchoscopy [biopsy was repeated for every site that was abnormal on previous bronchoscopy]. Biopsies were immediately formalin fixed and paraffin embedded.

Follow-up: All patients included in the study underwent follow-up WLB and AFB every 4-6 months. Chest CT was performed at baseline, at 6 mo and then every 12 months (Fig. 1).

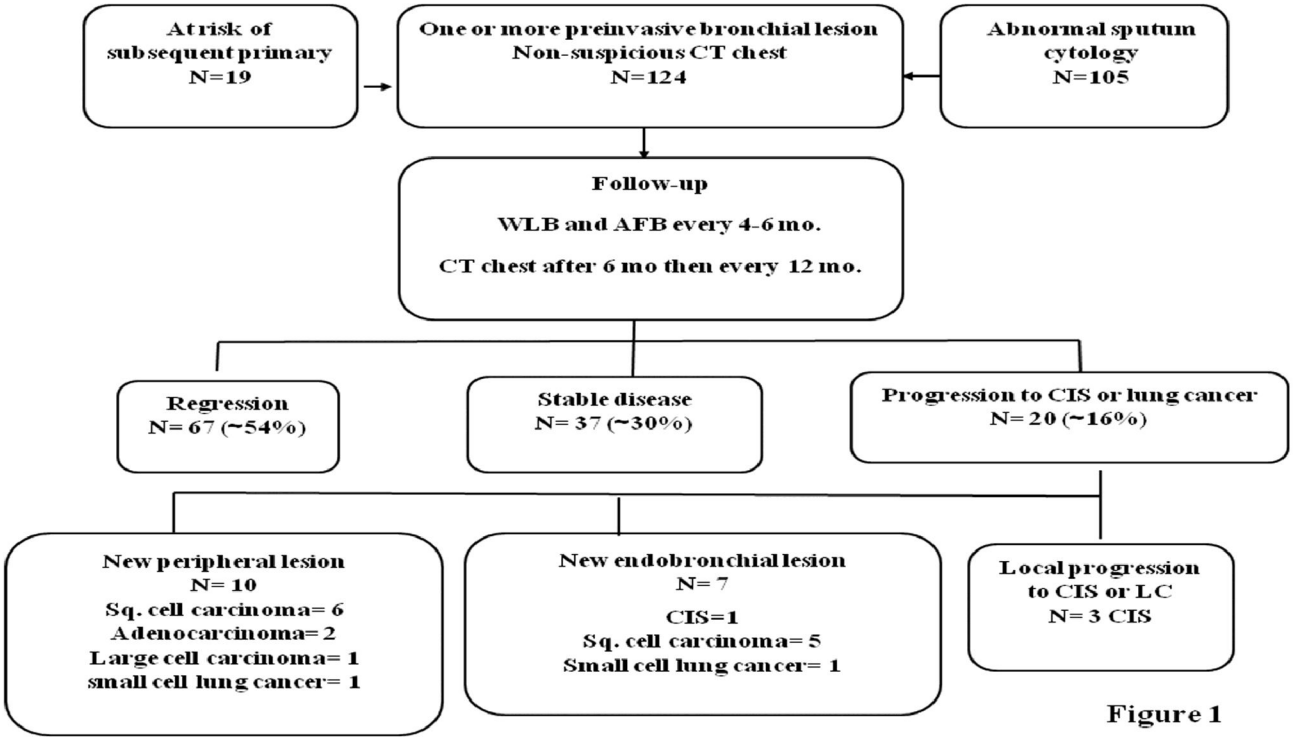

Fig 1. Follow-up protocol and outcome for 124 patients with bronchial preinvasive lesions followed-up by White light bronchoscopy (WLB), Autofluorescence bronchoscopy (AFB) and chest computed tomography (CT). Progression was defined as the development of CIS or LC; regression to squamous metaplasia or less severe lesion was considered regression; patients with mild, moderate or severe dysplasia at last follow-up were considered to have stable disease.
The lowest part shows histopathology for 20 detected carcinoma in in situ (CIS) and lung cancer (LC) lesions.

Endpoints were the development of CIS or LC (when diagnosed, CIS lesions underwent endoscopic treatment, which modify their natural course). Follow-up course was assessed for each individual according to the highest grade lesion at last follow-up: Progression was defined as the development of CIS or LC; regression to squamous metaplasia or less severe lesion was considered regression; patients with mild, moderate or severe dysplasia at last follow-up were considered to have stable disease.

Histological evaluation of bronchial biopsies: Bronchial biopsy specimens were reviewed by two pathologists according to the 1999 WHO criteria for preinvasive bronchial lesions.[17] Biopsies were classified as follows: normal or inflammatory, basal cell hyperplasia (BCH), squamous metaplasia (SM), mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ (CIS) and squamous cell carcinoma.

Statistical analysis: All statistical analyses were per patient based analysis, Mann-Whitney U test was used to compare the follow-up times. Comparisons were performed using Chi-square tests and bilateral Fisher test with Yates correction when required. Cox regression was used for multivariate analysis. For all tests, a difference with a $P< 0.05$ was considered statistically significant.

Progression free interval was calculated from the date of

first bronchoscopy to the date of CIS or LC diagnosis. Cumulative risk of progression was determined from a Kaplan-Meier plot.

Analyses were done using SPSS software version 12 (SPSS Inc., Chicago, IL).

RESULTS

Among 124 patients with 240 preinvasive bronchial lesions, 20 CIS or LC lesions were detected during follow-up in 20 (16%) patients, 7 were detected as new endobronchial lesions, 10 as new peripheral lesions and 3 as local progression from severe dysplasia to CIS. The median time to progression was 24 months (range: 6-54 mo). Cumulative risk of progression was 7% at one year, 20% at three years and 44% at 5 years (Fig. 2). Among detected lung cancers, 80% were stage 0 or stage I and underwent treatment with curative intent. The other 4 cases included 2 with small cell lung cancer, one adenocarcinoma with hematogenous metastasis and one with a second primary squamous cell carcinoma who underwent completion pneumonectomy. Histological diagnosis of progression lesions is shown in (Fig. 1).

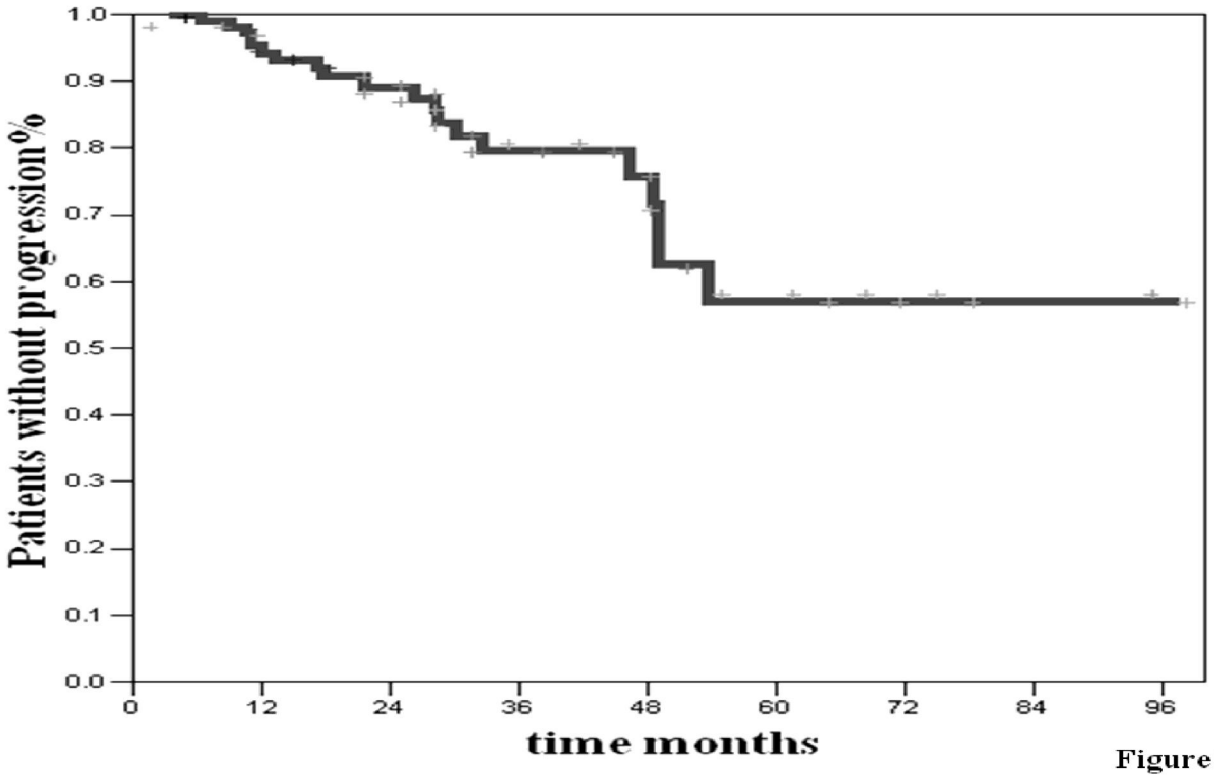

Figure 2

Fig 2. Kaplan-Meier plot for the Progression-free interval of 124 patients with preinvasive bronchial lesions.
Progression-free interval was measured from the date of first bronchoscopy to either the date of carcinoma in situ (CIS), lung cancer diagnosis or the last follow-up date.

The median follow-up duration was 20.4 mo, mean follow-up time was 26.8 mo. (range:4-98 mo) for the study population. Follow-up duration for patients with regression, stable disease and progression to CIS or LC (mean ± SD) were, 25 ± 18.4, 30 ± 25.4 and 26±15.7 mo, respectively, with no significant difference (P = 0.46). Histology of preinvasive bronchial lesions detected at baseline and during follow-up is shown in Table 2.

Table 2. Pathological grade of baseline and follow-up new preinvasive lesions.

	Baseline lesions	Follow-up new lesions	Total
Total number of preinvasive bronchial lesions	176 (73%)	64 (27%)	240
Mild dysplasia	55 (75%)	18 (25%)	73
Moderate dysplasia	99 (71%)	40 (29%)	139
Severe dysplasia	22 (79%)	6 (21%)	28
Preinvasive bronchial lesions per patient	1.42	0.52	1.94

Baseline and new SD lesion distribution according to risk factors. Detection of new preinvasive lesions during follow-up was insignificantly associated with patient smoking status or smoking >52 or ≤ 52 pack-year. (p = 0.095 and p = 0.486; Table 3. The number of dysplasia detected in COPD patients was greater than for non-COPD, and they were more susceptible to the appearance of new SD during follow-up (p = 0.004 and p = 0.009, respectively; Table 3. Difference between patients with high and low grade lesions with regard to development of new SD during follow-up, 44.4% (8/18) and 34.9% (37/106), respectively, was statistically insignificant (p= 0.43; Data not shown).

Table 3. Patients (N = 124) grouped according to risk factors and baseline, new (squamous dysplasia) SD lesions.

	≥ 2 baseline SD, No (%)	P value	≥ one new SD, No (%)	P value
Medical History				
Abnormal sputum cytology (105)	39 (37.1)	0.364	40 (38.1)	0.326
At risk of subsequent primary (19)	5 (26.3)		5 (26.3)	
Smoking history				
Current smokers (90)	32 (35.6)	0.203	37 (41.1)	0.095
Ex-smokers (29)	12 (41.4)		8 (27.6)	
Non-smokers (5)	0 (0)		0 (0)	
Pack-year				
≤52 (63)	20 (31.7)	0.377	21 (33.3)	0.486
>52 (61)	24 (39.3)		24 (39.3)	
COPD status				
COPD (64)	27 (42.2)	0.107	31 (48.4)	0.004
Non-COPD (60)	17 (28.3)		14 (23.3)	

Progression to CIS or LC. Patients with new SD during follow-up were at higher risk to develop CIS or LC (p= 0.01 and p= 0.0001, respectively; (Fig. 3). COPD patients and smokers with > 52 pack-year smoking index had higher risk for progression than non-COPD patients and smokers with ≤ 52 pack-year (p= 0.001 and p=0.042, respectively; Table4). Although patients with high grade lesions (27.8%; 5/18) tended to progress to CIS or LC more frequently than patients with low grade lesions (14.2%; 15/106), this was statistically insignificant (p= 0.146; Table 4).

Results of multivariate Cox regression analysis controlling for other risk factors showed that, COPD is an independent risk factor for LC in patients with bronchial SD, Relative risk (RR) and 95% confidence interval (95% CI) were [4 (1.13- 14.1) p= 0.031] for COPD, 1.8 (0.6-5.6) p= 0.286 for lesion grade, 1.2 (0.5- 3.2) p= 0.672 for multiple baseline SD, 1.3 (0.5- 3.5) p=0.559 for new lesion detection during follow-up, and 2.4 (0.9- 6.5) p= 0.081 for pack-year index>52.

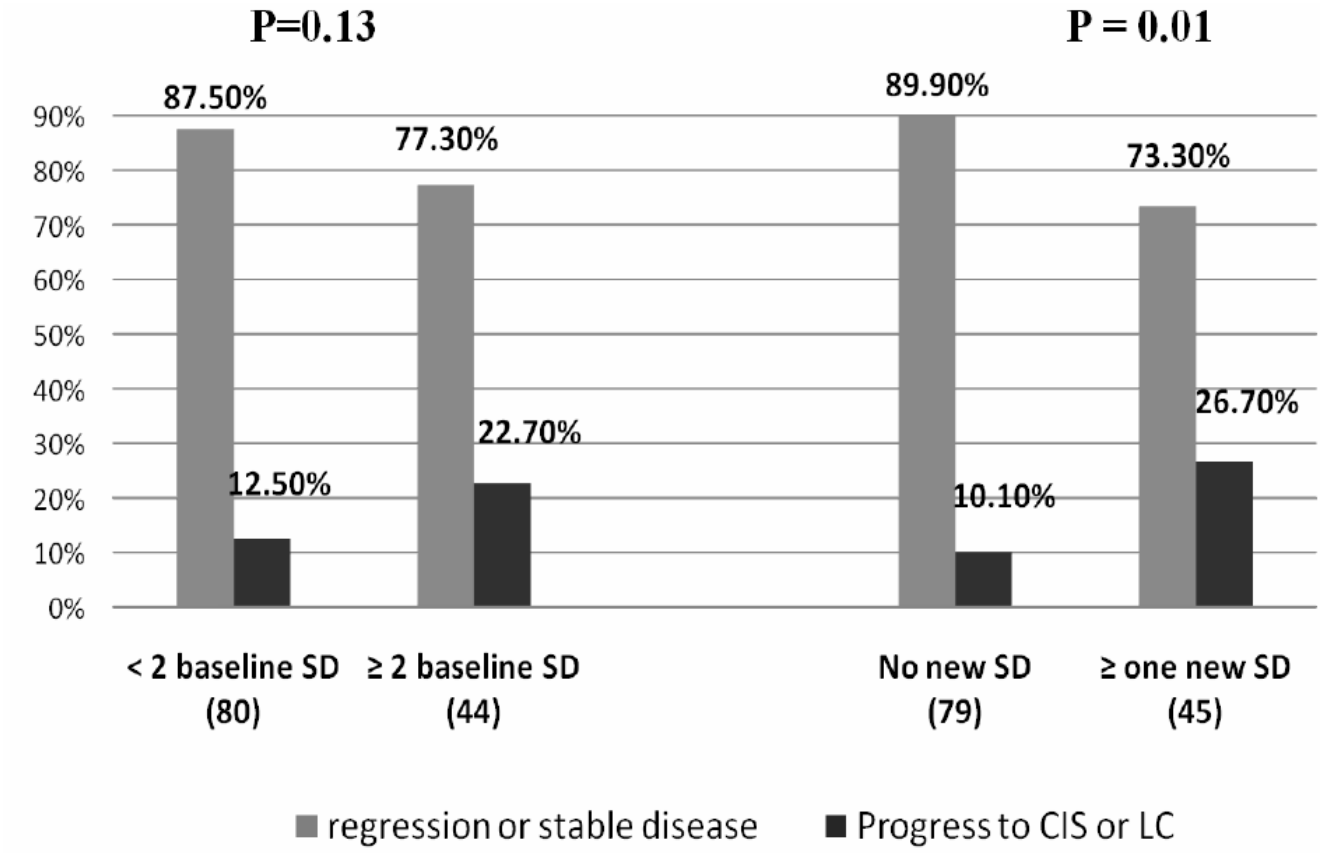

Fig 3. Comparison between rate of progression to carcinoma in situ (CIS) or lung cancer (LC) for patients with multiple baseline, follow-up new bronchial squamous dysplasia and their parallel groups.

Table 4. Progression to carcinoma in situ (CIS) or lung cancer (LC) according to risk factor and baseline lesion grade.

	Regress or stable N (%)	Progress to CIS or Lung cancer N (%)	
Medical History			
Abnormal sputum cytology (105)	89 (84.8)	16 (15.2)	0.508
At risk of subsequent primary (19)	15 (78.9)	4 (21.1)	
Smoking history			
Current smokers (90)	73 (81.1)	17 (18.9)	0.335
Ex-smokers (29)	26 (89.7)	3 (10.3)	
Non-smokers (5)	5 (100)	0 (0)	
Pack-year			
≤52 (63)	57 (90.5)	6 (9.5)	0.042
>52 (61)	47 (77)	14 (23)	
COPD status			
COPD (64)	47 (73.4)	17 (26.6)	0.001
Non-COPD (60)	57 (95)	3 (5)	
Lesion grade			
Low grade (106)	91 (85.8)	15 (14.2)	0.146
High grade (18)	13 (72.2)	5 (27.8)	

DISCUSSION

The present study found that, in a cohort of patients with preinvasive bronchial lesions, follow-up by AFB and chest CT has the potential to detect LC at early stages when treatment with curative intent is feasible. Although most preinvasive bronchial lesions will regress or remain stable, patients harboring these lesions are at high risk for LC.

In support of the field cancerisation theory,[18-20] we found that patients with new SD detected during follow-up were at higher risk for CIS and LC. Also, most (17/20) of the detected LC developed at sites different from the follow-up sites. Similar to this study, George et al[15] found that incidental LC detected by CT (5/11) was more frequent than direct progression of bronchial dysplasia.(4/11) Loewen et al found that patients with peripheral pulmonary nodules were 3.16 times more likely to exhibit pre-malignant changes on AFB.[21] And, Pasic et al found that multiple suspicious lesions detected by AFB predicted malignant transformation.[22]

Previous studies on the natural history of preinvasive lesions have used biopsy and to determine the histologic grade of these lesions. However, biopsy involves disruption and removal of a proportion of the lesion. The effect of this disruption and its impact on the natural history of the lesion under investigation is not known.[14] Additionally, preinvasive lesions are often small, and may be completely removed during biopsy; this suggests that the results of previous studies on the natural history of preinvasive lesions may have been compromised by biopsy.[14,23] The effect of biopsy will not be known until accurate, reproducible methods using non-invasive means are developed for lesion classification.[24]

In the meantime, detection of new preinvasive lesions during follow-up is an available option to address natural progression from apparently normal bronchial mucosa, which may carry a genetic aberration, to dysplastic epithelium. Detection of new preinvasive lesions was previously reported by George et al,[15] as 11 of 36 high grade and 5 of 17 low grade lesions were detected during follow-up at sites that had previously been judged to be normal. Also, Sin et al[25] detected new SD in 15/65 patients during a 6 month follow-up. However, to our knowledge, the current investigation is the first to describe an association between detection of new preinvasive lesions and increased risk for LC.

Similar to the current study, a number of studies have shown that chronic obstructive pulmonary disease (COPD) is an independent risk factor for LC.[26-28] The incidence of LC is 2 to 5 times greater in smokers with chronic bronchitis or emphysema than in smokers without COPD.[9] In addition, an inverse relationship between the degree of airway obstruction and the risk of LC has been demonstrated.[26-28]

A study by Chien et al. of heavy smokers with asbestos

exposures showed that a baseline FEV1/FVC ratio < 0.7 was significantly associated with an increased risk of developing LC, even when baseline FEV1 was > 80%. LC risk among those with baseline airflow obstruction and FEV1 < 60% was 4-fold higher than among those without baseline airflow obstruction and FEV1 >80% ($p<0.001$).[28]

The mechanisms by which the risk of developing neoplastic disease increases with COPD are not clear, although several recent publications suggested that inflammation and associated oxidative and nitrosative stress could account for carcinogenesis in COPD patients. During inflammation, enhanced ROS/RNS production may induce recurring DNA damage, inhibition of apoptosis and activation of proto-ontogenesis by activating certain signal transduction pathways.

Thus, it is conceivable that chronic inflammation-induced production of ROS/RNS in the lung may predispose individuals to LC.[29,30]

In our cohort of 124 patients with 240 preinvasive bronchial lesions, on a per patient analysis basis, progression rates of patients harboring high or low grade lesions were 27.8% and 14.2%, respectively. Breuer et al[31] reported 39% and 26% progression rate of high and low grade lesion patients, while George et al[15] found that 56% of patients with high grade lesions developed LC and none of their patients with low grade lesion developed LC. respectively.

The reason for these discrepancies of progression rates, as well as the association of progression with patient clinical criteria, including smoking history and COPD status.[15,31-35] could be attributed to one or more of the following. First, difference in risk distribution in study population, the proportion of patients with abnormal sputum cytology, history of aerodigestive cancer, occupational exposure, COPD and patients with symptoms are different between studies.[11] Second, interobserver variability in interpretation of lesion grade, especially discrimination between mild and moderate dysplasia, and between severe dysplasia and CIS.[14,36] Third, the difference in follow-up time interval, ranging from 3 months to 12 months. Thus, mild dysplasia followed up every 12 mo may gradually progress during this time interval to the next biopsy.

However, severe dysplasia during the same time interval would be subjected to the traumatic effect of biopsy three times, while this could affect the natural course or not require further investigation. Fourth, difference in definition of progression, and follow-up end point, either two step progression, CIS, microinvasive or invasive cancer.[14,15] Fifth, difference between mean patient follow-up duration. Sixth some studies only used AFB follow-up, while others used combined AFB and CT. Finally, the effect of repeated biopsy, which may explain the previously reported non-stepwise changes of preinvasive bronchial lesions.[31]

Although the use of two AFB devices, namely LIFE and AFI, could be a limitation to our study, previous reported findings showed that AFI has more specificity for detection of preinvasive lesions than LIFE, but no significant difference with regard to sensitivity, thus, AFI by its better specificity decreased the number of biopsies from areas of bronchitis that appear abnormal during LIFE bronchoscopy.[37]

Taken together, patients with preinvasive bronchial lesions, especially those with COPD, and new SD during follow-up, are at high risk of LC. AFB and CT follow-up facilitated early detection and treatment with curative intent. Newly emerging, non-biopsy endoscopic techniques, such as Optical coherence tomography,[24] fibered confocal fluorescence microscopy[38] and bronchial endo-cytoscopy,[39] will help us to better define the natural course of preinvasive bronchial lesions.

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Competing interests: None.

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