Synchronous invasive or preinvasive bronchial lesions detected by autofluorescence bronchoscopy in patients with lung cancer

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KEYWORDS
Lung cancer;
Synchronous;
Preinvasive bronchial lesions

Abstract  Objectives: In support with field cancerization theory, some patients with lung cancer (LC) will also have synchronous invasive or pre-invasive bronchial lesions. In this cross sectional – analytic study autofluorescence bronchoscopy (AFB) was used to assess the prevalence of synchronous lesions in patients with LC.

Materials and methods: All patients with abnormal sputum cytology underwent white light and AFB. From 335 patients with abnormal sputum cytology referred for AFB, lung cancer was detected in 91 patients (89 male and 2 female) of age (mean ± SD), 67 ± 8 years. 77 had squamous cell carcinoma (SqCC), 13 had adenocarcinoma and one patient with small cell lung cancer (SCLC).

Results: Synchronous lesions detected in 26 (29%) patients, 25 (33%) of patients with SqCC, one with adenocarcinoma, no synchronous lesion detected in one patient with SCLC. The most severe detected synchronous lesion was adenocarcinoma in one patient, Carcinoma insitu (CIS) in 4 patients, severe dysplasia in 3 patients, moderate dysplasia in 10 patients, and mild dysplasia in 8 patients. Synchronous lesions were more frequently detected in current smokers (35%), than in ex-smokers (20%) and non-smokers (15%).

Conclusion: Synchronous preinvasive lesions are frequent in patients with LC and AFB should be included in pre-operative evaluation of these patients.

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Introduction

The incidence of synchronous primary lung tumors is reported around 0.2–20% [1] and has been increasing recently due to the widespread use of imaging modalities such as multislice spiral computed tomography (CT), fluorescence endoscopy and positron emission tomography (PET) scanning. The simultaneous detection of more than one pulmonary nodule in patients with a lung cancer raises the clinical dilemma of whether these lesions represent intrapulmonary metastases that migrated
from the same origin or the secondary primary lung tumors. The criteria proposed by Martini and Melamed [2] in 1975 for the diagnosis of synchronous multiple primary lung tumors are still commonly used and are primarily based on the histological characteristics of the tumors, location, presence or absence of carcinoma in situ, vascular invasion, metastasis and other empirical features without the biological and molecular bases [3].

Up to 10% of patients successfully treated for primary NSCLC will develop a second primary lung cancer [1]. Since diagnosis of a synchronous primary tumor may affect the diagnostic work-up and definite therapy, precise diagnostic procedures are mandatory. Lung imaging fluorescence endoscopy (LIFE) has proven better than conventional white light bronchoscopy (WLB) for visualizing premalignant lesions or early stages of lung cancer [4–6]. However, Kurie et al [7] have cast a serious doubt on the sensitivity of LIFE and state that LIFE cannot replace conventional bronchoscopy, but should be used in addition to WLB. In this study, the prevalence of preinvasive bronchial lesions in patients with lung cancer was estimated, and its impact on definite outcome of the patients was evaluated.

Patients and methods

Patients

This cross sectional – analytic study was conducted as part of Japan lung cancer (LC) early detection program, in which patients at high risk for LC underwent screening by sputum cytology; persons with abnormal sputum cytology were subjected to autofluorescence bronchoscopy.

From 335 consecutive patients at risk of LC with abnormal sputum cytology and underwent AFB examinations at Chiba University Hospital, Chiba, Japan during the period from December 1999 to December 2008, 91 patients (89 men and 2 women) were included in the current study. Patients eligible for this study had LC (non small cell lung cancer or small cell lung cancer).

Patients’ median age was 68 (mean ± SD, 67 ± 8 years). A patient was considered an ex-smoker if he/she had stopped smoking for more than 1 year. All patients underwent white light (WLB) and autofluorescence bronchoscopy (AFB).

Bronchial biopsy specimens were reviewed by 2 pathologists according to the WHO 1999 criteria for pre-invasive bronchial lesions [8]. Biopsies were classified as follows: normal or inflammatory, basal cell hyperplasia (BCH), squamous metaplasia (SM), mild dysplasia, moderate dysplasia, severe dysplasia, CIS or squamous cell carcinoma [8].

Endoscopy

WLB was done using a flexible video bronchoscope (BF-240, Olympus Optical Corporation, Tokyo, Japan 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 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 Corpora-

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS software version 12) (SPSS Inc., Chicago, IL). Comparisons were made by Chi-square tests and bilateral Fisher test, with Yates correction when required. P < 0.05 was considered statistically significant.

Results

The current study included 91 patients, 89 male and 2 females, smoking status is shown in Table 1 and 77 patients had squamous cell lung cancer (SQCC), 13 had adenocarcinoma while one patient had small cell lung cancer (SCLL) (Table 1).

Synchronous lesions were detected in 25 patients (28%), 7 patients had mild dysplasia as the most severe synchronous lesions, 10 patients had moderate dysplasia, 3 patients had severe dysplasia, 4 patients had carcinoma in situ and one patient had adenocarcinoma as the most severe detected Table 1: demographic data and primary diagnosis synchronous lesion (Table 2).

Number of patients with synchronous lesions according to their primary lung cancer diagnosis is shown in Table 3 and the distribution of detected synchronous lesions for each lung cancer type is shown in Table 4.
Synchronous lesions were more frequently detected in current smokers compared to ex-smokers and non-smokers and this was significant \((P < 0.05)\) as shown in Table 5.

### Discussion

In the current study we found that the presence of synchronous invasive or preinvasive bronchial lesions is a frequent finding in patients with lung cancer and this was more significant among current smokers compared to non-smokers and ex-smokers. More than 50 years ago, Slaughter et al. [9] noted that smokers developed multiple preneoplastic lesions and synchronous (i.e., those detected simultaneously) or metachronous (i.e., those detected within a relatively short period) tumors in the squamous epithelium of the oral cavity, a phenomenon they termed “field cancerization.” They attributed these findings to tobacco carcinogens damaging the entire field at risk – the oral mucosa. Several years later, Strong et al. [10] extended this concept (and the clinical implications) to the entire upper aerodigestive tract. Multifocal primary tumors having a similar histological appearance have been described in many organs but are especially common in lung cancer. Wang et al. [11] investigated the mechanisms by which these tumors arise. The results of these studies pose both important biological and clinical management questions. Smokers cured of one aerodigestive cancer, including lung cancer, are at greatly increased risk of developing a second primary malignancy [12]. This event may occur several years later, may involve tumors of differing histological types, or the tumors may arise in different anatomical regions of the field (such as the larynx and lung). The origin of these tumors has been attributed to a “field” effect. More controversial are multifocal tumors of similar histology that arise synchronously or metachronously in the same organ. Multifocal tumors may be localized to multiple (satellite) nodules within a small region of the lung, involve a single lobe or multiple lobes within a single lung, or be present in both lungs. Two major mechanisms have been proposed by which histologically similar multifocal tumors arise: (1) a single clonal event resulting in a tumor that subsequently spreads within one or both lungs and (2) multiple tumors are arising independently in a carcinogen damaged field.

Nearly 30 years ago, Martini and Melamed [2] suggested clinicopathological criteria to help identify the origin of multifocal tumors. However, their criteria are guidelines for making clinical decisions, not definitive proof of origin. Martini and Melamed wished to provide guidance for lung cancer surgery; if the two lesions were thought to be separate lung cancers, they should be treated “independently” (and resected as such). By contrast, if they were thought to represent metastases, this could be taken as an indication of an unresectable disease. Laboratory investigations to distinguish between these possibilities have resulted in multiple publications for more than 20 years. Many of these publications do not specifically address the question at hand, the sheer number of reports indicate substantial interest in the subject. Wang et al. [11] have studied two or more synchronous or metachronous tumors \((n = 70)\) found in 30 patients undergoing resection(s) for lung cancer at multiple centers. However, the investigators do not tell us the frequency of multifocal tumors in their series. In ear-

### Table 3  Detected synchronous lesions according to primary lung cancer.

<table>
<thead>
<tr>
<th>Primary lung cancer</th>
<th>No. of patients with synchronous lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma (77)</td>
<td>25 (33%)</td>
</tr>
<tr>
<td>Adenocarcinoma (13)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Small cell lung cancer (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 4  Frequency and grade of detected synchronous lesions.

<table>
<thead>
<tr>
<th>Lesion grade</th>
<th>0 (%)</th>
<th>Mild dysplasia (%)</th>
<th>Moderate dysplasia (%)</th>
<th>Severe dysplasia (%)</th>
<th>Carcinoma in situ (CIS) (%)</th>
<th>Adenocarcinoma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous (76)</td>
<td>52 (69%)</td>
<td>6 (8%)</td>
<td>10 (13%)</td>
<td>3 (4%)</td>
<td>4 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Adenocarcinoma (13)</td>
<td>12 (92%)</td>
<td>1 (8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Small cell carcinoma (1)</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>7</td>
<td>10</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 5  Detection of synchronous lesions according to smoking status.

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Presence of Synchronous lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
</tr>
<tr>
<td>Non-smoker (6)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Ex-smoker (34)</td>
<td>28 (82%)</td>
</tr>
<tr>
<td>Current smoker (51)</td>
<td>32 (71%)</td>
</tr>
</tbody>
</table>
findings reflect a rising incidence, as has been suggested [18], with lung cancer and it is more frequent in current smokers.

In Flieder et al. [19] study, multifocal adenocarcinomas were identified in 15 of 77 (approximately 20%) resections for CT screening – identified lung cancers. Thus, this clinical problem is likely to become a common event with the widespread application of CT-based screening programs. In addition Van Rens [20] studied the additional value of using autofluorescence bronchoscopy for the evaluation of patients with lung cancer, the study included, sixty-nine patients with NSCLC and three patients had small cell lung carcinoma. Apart from the primary lesion, one up to six additional endobronchial lesions were visualized in 48 patients by WLB and/or LIFE. High-grade dysplastic lesions were detected in ten patients, three of whom were eligible for surgery of the primary tumor after completion of the investigations. Three other patients (4.3%) had synchronous cancers (NSCLC). In one patient, the lesion was visualized by LIFE and by WLB. The other two malignant lesions were detected only by LIFE. In these three latter patients, diagnostic work-up and definite treatment was changed, as a result of detection of synchronous lesions. In concordance with these data, in the current study by Van Rens [20] studied the additional value of using autofluorescence bronchoscopy for the evaluation of patients with lung cancer we found that synchronous invasive or preinvasive bronchial lesions are a frequent finding in patients with lung cancer and it is more frequent in current smokers.

Conclusions

Synchronous preinvasive lesions are frequent in patients with LC and AFB should be included in pre-operative evaluation of these patients. The use of AFB for preoperative evaluation of patients with lung cancer is recommended.

Conflict of interest

No conflict of interest.

References