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Autofluorescence bronchoscopy for lung cancer surveillance based on risk assessment

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Summary

Introduction: This is a preliminary report of an ongoing prospective bimodality lung cancer surveillance trial for high-risk patients. Bimodality surveillance incorporates autofluorescence bronchoscopy (AFB) and spiral CT (SCT) in high-risk patients as a primary lung cancer surveillance strategy, based entirely on risk factors. AFB was used for surveillance and findings were compared with conventional sputum cytology (CSC) for the detection of malignancy and premalignant central airway lesions.

***Eligibility*:** For eligibility, patients were required to have at least two of the following risk factors: 1) $\geq$ 20 pack year history of tobacco use, 2) asbestos-related lung disease on chest radiograph, 3) COPD with an FEV-1 < 70% of predicted, and 4) prior aerodigestive cancer treated with curative intent, with no evidence of disease for > 2 years. All eligible patients under went AFB, a low dose SCT of the chest without contrast, and a sputum sample was collected for cytology. Bronchoscopy biopsy findings were correlated with sputum cytology results, SCT-detected pulmonary nodules and surveillance-detected cancers. To date, 186 have been enrolled with 169 completing the surveillance procedures.

***Results*:** 402 patients registering at Roswell Park Cancer Institute (RPCI) were evaluated with spirometry, chest x-ray, history and physical examination, of which 207 were deemed eligible for the study. 13 lung cancers (7%) were detected in the 169 subjects who have completed all three surveillance studies to date. Premalignant changes were common and 66% of patients had squamous metaplasia or worse. CSC missed 100% of the dysplasia and 68% of the metaplasia detected by AFB, and failed to detect any cases of carcinoma or carcinoma in situ in this patient cohort. CSC exhibited 33% sensitivity and 64% specificity for the presence of metaplasia. Seven of 13 (58%) lung cancers were stage Ia or less, including 3 patients with squamous cell carcinoma. Patients with peripheral pulmonary nodules identified on SCT of the chest were 3.16 times more likely to exhibit premalignant changes on AFB ($p < 0.001$).

***Conclusion*:** Bimodality surveillance will detect central lung cancer and premalignancy in patients with multiple lung cancer risk factors, even when conventional sputum cytology is negative. In high-risk patients, AFB should be considered, regardless of sputum cytology findings.

Keywords

Auto-fluorescence bronchoscopy
Spiral CT
Chronic obstructive pulmonary disease
White light bronchoscopy
Risk assessment
Surveillance

1. Introduction

Lung cancer has no validated early detection strategy that is currently applied to populations at risk. However, more people die from lung cancer than from the aggregate of the four other major cancers (breast, colon, prostate, and cervical), in which early detection strategies are applied [1]. Overall, squamous cell lung cancer represents approximately 25% of lung cancer and it is believed that reversible preinvasive epithelial proliferation and squamous cell carcinoma in situ precedes its arrival [2]. While retrospective attempts at CT-based imaging of early central airway cancers have been reported [3], the detection of early squamous cell carcinoma has not been a common feature of CT-based screening trials [4-5], even when these trials are complemented by sputum cytology. In addition, the identification of frank carcinoma in sputum for the purpose of diagnosis has failed to reduce lung cancer mortality in randomized controlled trials [6].

In 1993, Lam et al reported the early detection of central lung cancer using an autofluorescence bronchoscopy imaging system (AFB). Using the fluorescence system in conjunction with a conventional white light bronchoscopy (WLB), they found that AFB doubled the detection of dysplasia and carcinoma-in-situ in 328 biopsies in 94 subjects. Moreover, 15% of patients in this study with known lung cancer were found to have synchronous carcinoma-in-situ (CIS) [7]. A subsequent non-randomized multicenter trial compared AFB to WLB in 173 patients at 9 institutions [8] and found that AFB plus WLB was twice as sensitive in the detection of carcinoma-in-situ or severe dysplasia when compared with WLB alone. These findings have been supported by numerous authors [9-12]. A recent large European randomized controlled multicenter trial [13] confirmed that WLB plus AFB was clearly superior to WLB alone for the detection of preneoplastic lesions.

Even though autofluorescence imaging improves the bronchoscopist's ability to detect preneoplastic lesions and intraepithelial neoplasms, AFB has not been integrated as an entry strategy into SCT based screening initiatives for lung cancer. While the term "screening" implies application of a test to a broad population [14], the term "surveillance" means "close observation of a person or group, especially one under suspicion" [15], and implies a more focused detection strategy applied to a narrower high-risk population. Evidence supports the use of AFB in patients with severe atypia or malignant cells in their sputum cytology [16], however we reasoned that certain high-risk individuals might be likely to have early central lung cancer or premalignancy, even if their sputum was negative, or if they were unable to produce sputum. These individuals might benefit from AFB based on risk-factors alone. The objective of our study was to compare the sensitivity of conventional sputum cytology with AFB and to correlate AFB bronchoscopy findings with SCT findings in the setting of a prospective surveillance trial for patients who were at risk for the development of lung cancer. We examined the null hypotheses that 1. AFB was equivalent to sputum cytology for the detection of premalignant lesions (metaplasia,

dysplasia and carcinoma-in-situ) and that 2. AFB plus SCT would be equivalent to SCT alone for the detection of lung cancer in high risk patients.

2. Methods

2.1. Patient population and recruitment

The High Risk Screening Cohort at Roswell Park Cancer Institute (RPCI) was established in 1998. This surveillance initiative incorporates an epidemiologic questionnaire, physical examination, and chest radiograph for patients who are at risk for lung cancer. High risk patients have been recruited from several sources: 1) asbestos litigation firms refer asbestos clients with radiographically confirmed asbestosis for medico-legal evaluation at RPCI; 2) patients with surgically treated aerodigestive tract cancers who are disease-free for greater than two years are referred by the department of surgery at RPCI for evaluation in the lung cancer surveillance program; and 3) community patients with moderate or severe chronic obstructive pulmonary disease (COPD) and are referred by pulmonologists and primary care physicians in the community for evaluation in the lung cancer surveillance program. Initial chest radiographs were reviewed by the physician at the time of enrollment (GL) and were not reviewed by a B reader. The outreach effort associated with this prevention and surveillance program has included public speaking, press releases, media interviews and the production of a color brochure that is distributed to local pulmonary and oncology offices in the community.

2.2. Initial patient evaluation

The initial medical history included assessment of the intensity and duration of tobacco use, history of asbestos exposure, and history of prior tobacco-related malignancy. All patients underwent a detailed history and physical. In addition, each completed a detailed epidemiological questionnaire and donated blood, buccal cell and induced sputum samples. The questionnaire collected detailed information on subject demographics, medical history, prescription and non-prescription drug use, lifestyle exposures (mainly tobacco and tobacco-product exposures and dietary exposures), diet, height, weight, use of alcohol, work history/occupational exposures, physical activity, reproductive and family history. A Thoravision ^{TM} (Phillips Medical Systems NA, Bothel, Washington) chest x-ray (CXR) was performed to document the presence of asbestos-related lung disease. Spirometry was performed in the initial clinic visit with a hand-held pneumotach spirometer (Easyone Diagnostic Spirometer, Medical Technologies, Chelmsford MA). Subjects were asked to perform at least three acceptable FVC (forced vital capacity) maneuvers, and at least 2 efforts were required to demonstrate reproducibility within 200 ml per the American Thoracic Society (ATS) standards. The maneuver that produced the greatest sum of the FVC and forced expiratory volume (FEV_1) was accepted as the baseline value. FEV-1 was interpreted using the predicted equations reported by Knudson [17].

2.3. Patient eligibility

In order to be eligible for the surveillance program, patients must have demonstrated at least 2 of the following risk factors: 1) radiographically documented pulmonary asbestosis or asbestos-related pleural disease; 2) a

history of previously treated aerodigestive tract cancer with a disease free interval of greater than 2 years; 3) a cigarette smoking history ≥ 20 pack years in intensity; and 4) COPD with a documented FEV_1 < 70% of predicted. Patients must have also been willing and able to give informed consent and agree to undergo AFB and SCT surveillance. Patients were excluded if they were not able to medically tolerate the AFB or SCT and if they were unable to medically tolerate therapy for lung cancer, including video-assisted thoracic surgery (VATS), radiotherapy and/or endobronchial therapy including photodynamic therapy (PDT). If the patient was found to be eligible for the study, they were provided with informed consent, and were offered enrollment into this prospective surveillance trial approved by the RPCI Institutional Review Board.

2.4. Sputum cytology

Initially, patients were asked to collect early morning samples of sputum for three consecutive mornings, just prior to their return visit to the clinic. Spontaneous pooled sputum was obtained in the first 40 patients. Due to the high proportion of these samples that were classified as insufficient for cytology, the protocol was changed to require sputum induction using hypertonic saline even if a productive cough was present. Prior to sputum induction, spirometry assessments were performed to provide a baseline quantitative measure of lung function and for safety monitoring during sputum induction. Sputum was obtained the remaining subjects by tidal inhalation of hypertonic (3%, 4%, 5%) saline at 7-minute intervals by ultrasonic nebulizer. If the baseline FEV_1 was < 1.0 liter, only isotonic saline (0.9%) was administered. Sputum samples were stored at 4°C until processing, for a period that did not exceed 2 hours. Sputum samples were treated with Sputolysin® (Behring Diagnostics, Somerville NJ) to lyse sputum plugs, and pen/strep solution to inhibit bacterial growth. The study cytologist (EN) at RPCI reviewed a cytology slide made on each sputum sample.

2.5. Bronchoscopy

AFB was performed on an outpatient basis with conscious sedation and local anesthesia by a single pulmonologist (GL), using the LIFE I system (Xillix Technologies Corp, Richmond, BC). As per our standard practice, the airways were examined by WLB, and then by AFB and visual findings were classified as normal, abnormal and suspicious, as described by Lam [8]. Endobronchial muscosal biopsies were taken from all abnormal areas, and from suspicious areas when possible, whether noted on either WLB or AFB imaging. In addition, surveillance biopsies of normal appearing epithelium were taken in all patients including those with normal appearing bronchial mucosa. This resulted in 3-6 biopsies were taken during the bronchoscopy procedure on average. Overall, the location of the biopsies was driven by the fluorescence and white light appearance and not according to predetermined sites.

2.6. Spiral CT of the chest

Non-enhanced spiral CT scan (SCT) of the chest was performed within a month of chest radiography with the GE LightSpeed Plus or the LightSpeed QXi (GE Healthcare, Milwaukee, WI). Images were acquired with 1.25 mm thickness

slices that were available for review at the workstation and were filmed at 2.5 mm slices. Clinically significant parenchymal pulmonary abnormalities identified by SCT scan were referred for contrast-enhanced CT scan of the chest consistent with accepted algorithms [4]. RPCI staff radiologists, who were blinded to current chest x-ray results, interpreted all SCT results.

2.7. Statistics

We assumed that 5% of enrolled patients would exhibit endobronchial preneoplasia, and that at least 56% of disease would be detectable with either AF bronchoscopy or sputum cytology. We also assumed that AF bronchoscopy would detect all cases detected by sputum cytology, and that AF bronchoscopy would detect preneoplasia twice as well as sputum cytology. Using McNemar's test, the estimated number of subjects to achieve 90% power with these assumptions was N = 208, with alpha = 0.05. Data analysis was performed using STATA 9.0 [18]. Proportions, odds ratios, 95% confidence intervals and p-values were also calculated to determine differences between tests. McNemar's test was applied to the proportions predicted by each test. A sensitivity and specificity analysis was performed comparing the results of sputum cytology to AFB.

3. Results

To date, 402 patients have been evaluated for the study. A total of 207 proved to be eligible and 186 were enrolled. A total of 169 of the 186 enrolled patients have completed all of the surveillance procedures and are included in this data analysis. Accrual nears the target of 208, and ongoing surveillance continues with a follow up range of 3-16 months. Sputum induction with saline resulted in mild bronchospasm in 1 COPD patient who required treatment with bronchodilators. Seventeen patients cancelled bronchoscopy for personal reasons. AFB and SCT were completed on all other patients without unexpected complications.

(Table 1) summarizes the baseline characteristics of study participants, including referral sources.

Table 1 - Selected demographic and clinical characteristics of enrolled patients

Variable	***Frequency***
Referral source, %	
Physicians	45%
Asbestos attorneys	24%
Self-referred	27%
NYS Smoker's Quit Line	4%
Gender, male, n (%)	127 (70.6%)

Age, years, ***mean (SD)***	63.1 (9.05)
Age range, ***years***	37 to 83
Race, white, ***n (%)***	175 (97.2%)
Smoking status, n (%)	
Current	61 (34.2%)
Former	116 (65.2%)
Never	1 (0.6%)
Person years of smoking, ***mean***	58.0 PY
Asbestos exposed, ***n (%)***	70 (39.3%)
COPD diagnosed[1], ***n (%)***	117 (65.0%)
Prior Cancer	50 (29%)
Pulmonary symptoms at surveillance, n (%)	
None	16 (9%)
Dyspnea only	48 (27%)
Cough only	31 (17.4%)
Dyspnea and cough	65 (63.5%)
Others	18 (10.1%)

[1] Chronic obstructive pulmonary disease

Physician referrals provided the majority of patients (45%), with the remainder coming from asbestos litigation attorneys (24%), self-referrals (27%) and 4% from the New York State Smoker's Quit Line located at RPCI. The majority of patients were male (70.6%), white (97.2%), former smokers (65.2%) and on average, 63 years old. Approximately 39% exhibited asbestos-related lung disease on chest radiograph and 65% had a diagnosis of chronic obstructive pulmonary disease (COPD). Pulmonary symptoms from underlying pulmonary conditions were common, but did not correlate with the presence of cancer or premalignancy.

(Table 2) shows a summary of the results from the sputum, AFB and SCT tests.

Table 2 - Results of diagnostic studies of screened patients (n=169)

Diagnostic test	**Number**	**Percent**
Sputum		
Normal	73	67%
Metaplasia	35	32%
Dysplasia	1	1%
Insufficient	60	
Bronchoscopy		
Normal	28	17%

Inflammation	16	9.7%
Metaplasia	84	51%
Dysplasia	19	11.5%
CIS	2	1.2%
Cancer	3	1.8%
Other	18	10.7%
CT Nodules		
No	70	43%
Yes	85	52.1%
Non-solid opacities	8	4.9%

The majority of the sputum samples classified as "adequate" were cytologically normal (67%). Conversely, the AFB detected metaplasia as the worst grade lesion in 51% of the patients, while 11.5% had dysplasia and 3% showed carcinoma in-situ (CIS) or endobronchial cancer. Laryngeal carcinoma in situ was also identified in 2 patients. In addition, 52% of the chest SCT performed showed at least one peripheral nodule. Sputum cytology was not a reliable predictor of outcome of AFB in this cohort of high risk patients (Table 3).

Table 3 - Relationship between the detection of premalignancy with sputum cytology vs. AF bronchoscopy

Premalignancy*	Sputum positive	Sputum Negative	Total
Bronchoscopy*** Positive	26	52*	78
Bronchoscopy Negative	5	9	14
Total	31	61	92

* McNemar's significance probability = 0.0000

** = squamous metaplasia, dysplasia, or carcinoma-in-situ (distinguished by histopathology)

*** = suspicious appearance on fluorescence, prompting biopsy

The majority of patients with metaplasia or worse identified with AFB had normal sputum cytology. Of the patients with sputum cytologies that *were* positive for metaplasia, 83% showed a metaplasia or worse on AFB. In this patient cohort, the sensitivity of sputum to predict a metaplasia or worse histology on AFB was 33% (95% confidence intervals 22.23% - 44.10%), with a specificity of 64% (95% confidence intervals 35.14 – 87.24%), and the detection of premalignancy with AFB was significantly better (McNemar's p-value< .0001).

The 13 lung cancers identified in patients as part of this surveillance study, representing an overall rate of 7%. As shown in (Table 4), 7 of these cases (58%) proved to be diagnosed at stage 0 or 1a.

Table 4 - Surveillance-detected cancers detected on study

Cancer Cell Type	Stage	CT Result[1]	AF Bronchoscopy Result[1]	Treatment	Outcome Notes
Small cell	Limited disease	+	+	Chemotherapy radiation	Initial CR, PD at 24 months
Carcinoid	0	-	+	PDT [3]	NED[2] 3 years
Squamous cell	0	-	+	Electrocautery	NED[2] 28 months
Squamous cell	0	-	+	Electrocautery	Expired from MI at 24 months
Adenocarcinoma	Ia	+	-	Lobectomy	NED[2] 26 months
Adenocarcinoma	Ia	+	-	Lobectomy	NED[2] 11 months
Adenocarcinoma	Ia	+	-	Radiation	Expired at 16 months from metastatic disease
Adenocarcinoma	IIIb	-	-	Radiation	Expired: interval cancer
Adenocarcinoma	IV	+	-	Chemotherapy	Expired: metastatic renal cancer
Adenocarcinoma	IIIa	+	+	Chemotherapy Radiation	17 months post therapy
Squamous cell	Ia	+	-	Lobectomy Chemotherapy	Adjuvant chemotherapy 5 months post resection
Adenocarcinoma	IV	+	-	Thoracotomy	Expired 6 months
Non-small cell (neuroendocrine)	IV	+	-	Chemotherapy Radiation	Receiving treatment at 6 months

[1] (+) = cancer detected; (-) = no cancer detected

[2] NED = no evidence of disease

[3] PDT = photodynamic therapy

In 6 out of 7 adenocarcinoma tumors, a central airway premalignant lesion was present, and in all but two of cancer patients, as central airway premalignancy was detected. In addition, the presence of metaplasia or worse on AFB significantly increased the chance of finding at least one pulmonary nodule on SCT (OR = 3.15, 95% confidence interval = 1.66-6.41, p-value= .001) (Table 5).

Table 5 - Association between SCT detected nodule and AFB detected premalignant lesion

	SCT Nodule				
Premalignant Lesion	Yes	No	**OR**	**(95% CI)**	**P-value**
Yes	58	41	3.15	(1.66-6.41)	.001
No	13	12			

4. Discussion

We detected a 7% prevalence of lung cancer with bimodality surveillance in this cohort of high-risk patients. This figure is higher than reported disease prevalence in SCT-based screening trials, and we attribute this in part to risk assessment. Multifactorial risk modeling has been used in the setting of breast cancer [19], but advanced multifactorial models have not been validated in lung cancer. In our trial design, we reasoned that patients with more than one established risk factor could be expected to have greater risk for lung cancer than those with tobacco exposure alone. More recently, detailed risk models have been introduced [20] which should be incorporated into future surveillance trials. Even if bimodality surveillance lowers lung cancer related mortality, more predictive risk models will be needed for aggressive surveillance to become cost-effective [21]. Our data show that the clinical use of established risk factors permits a case selection that is relatively rich in premalignant and malignant events.

Although a trend towards increased detection was observed (p = 0.20) when AFB is added to SCT in high risk patients, we failed to reject the null hypothesis that bimodality surveillance is better than SCT alone. We believe that these findings are due to the sample size, and further study with a larger cohort will be necessary to show the clear superiority of a bimodality approach in high risk patients.

Although occult lung cancer is commonly detected with SCT in patients with negative CXR results [22], central squamous cell cancers are not usually detected with this method. Henschke et al. also reported on the use of SCT

scan in a prevalence study of 1,000 high-risk volunteers in which 27 cases of early stage lung cancer were detected. Of the 27 cases of lung cancer, only two patients had endobronchial disease and only 1 had squamous cell carcinoma [4]. In a more recent Mayo Clinic lung cancer screening trial that enrolled 1,049 participants, only 2/40 lung cancer cases were detected with sputum cytology alone and the rest were detected with low-dose SCT (LDSCT) [23]. Bechtel et al reported the use of sputum cytology combined with CT scans of the chest in 126 patients with COPD. Thirty-two percent of the cancers detected had positive sputum cytology, and 1 of these had a normal chest CT [24]. Squamous cell lung cancer represents approximately 25% of all lung cancer, and the squamous cell type represented 25% of surveillance-detected lung cancer in our cohort.

We found that AFB was well tolerated as a minor outpatient procedure, even in high-risk patients, consistent with other investigators [25]. Patients in our cohort were generally willing to undergo a repeat procedure if necessary, suggesting that AFB examination for the follow-up of high-risk lesions is also feasible. In the case of colorectal cancer screening, colonoscopy and flexible sigmoidoscopy have been recommended in the screening guidelines for early detection of occult carcinoma [26], [27], [28]. However, the impact of screening with flexible sigmoidoscopy on colorectal cancer mortality remains inconclusive [29]. Although randomized controlled data is ultimately needed to see if this approach reduces lung cancer related mortality, such data will not be available for many years. Existing current evidence does suggest however, that the prognosis of early central lung cancers generally have favorable survival characteristics, even when treated with endobronchial therapy [30]. For this reason, we believe that the early detection of curable central lung cancer with AFB should be employed in lung cancer surveillance algorithms for high risk patients.

Abnormal sputum cytology has been considered a classic indication for bronchoscopy. In the Mayo Clinic Lung Project, the sputum cytological presence of malignant cells did detect 15% of all lung cancers, almost all of which were squamous cancers [31]. Unfortunately, only 35/68 (51%) were carcinoma in situ or microinvasive carcinomas, while the rest had bronchial wall or cartilage invasion [32]. In two other randomized NCI-sponsored studies designed to evaluate the added value of sputum cytology to a screening chest radiographs strategy, sputum failed to reduce overall mortality in the screened group [33], [34]. Our preliminary results from the first 169 high-risk patients undergoing surveillance SCT and AFB found that certain high-risk patients can exhibit negative conventional sputum cytology and still harbor significant early malignant or premalignant changes in the central airway. Our findings differ from the findings of the European AFB trial [13], which did not detect severe dysplasia or carcinoma-in-situ in the subset of 56 patients that were pre-selected based on tobacco exposure plus COPD or occupational exposure. The presence of mild dysplasia or metaplasia in this patient group was not reported, however. The Colorado SPORE detected a 6% incidence (5/79) of central malignancy

with AFB in a subset of COPD patients with moderate atypia and negative chest radiographs [35]. Even in this experienced group with extensive experience in sputum collection and interpretation, 537/2550 eligible patients (21%) failed to submit at least 1 adequate sputum for examination [36] in a previous report. Our data suggest that the majority of such patients actually have metaplasia or worse. Sputum cytology is an inexpensive and noninvasive technique and it is likely that investigational techniques will eventually augment the sensitivity of sputum cytology. Our data rejects the null hypothesis that sputum cytology and AFB are equivalent for the detection of intraepithelial neoplasia: AFB clearly increased the detection rate of premalignancy (p= 0.0000). This finding implies that in patients with multiple risk factors for lung cancer, direct AFB is should be considered, where it is available. In this setting, the rate of cancer detection with AFB exceeds the cancer detection rate of colonoscopy surveillance in patients with positive fecal occult blood.

Even though we found a high prevalence of lung cancer in this relatively small cohort, the fraction of early cancers was much lower than what is described in most SCT trials [22], [36], [37], [38], and closer to the value found in a similar cohort of COPD patients [24]. The poor prognosis of these patients raises concerns regarding the ultimate limitation of lung cancer screening described as lead-time bias. In addition, we also found one interval cancer in a patient who had negative initial surveillance studies. The fraction of rapidly growing lung cancers represents a subset of patients who will not benefit from surveillance.

We found a remarkably high incidence of premalignant lesions in our high-risk cohort. We believe that the detection of preneoplastic lesions is clinically relevant. Breuer reported the follow up of 52 patients harboring 134 preneoplastic lesions were followed with serial AFB and found that 9% of metaplastic and 32% of severe dysplastic lesions progressed to malignancy [39]. The severity of dysplasia was not predictive of progression. In another study, Bota et al followed 104 patients with 416 lesions for over 2 years with serial AFB. In this cohort, 30% of metaplasia progressed to dysplasia (but 3 lesions progressed directly to carcinoma), and 37% of dysplastic lesions also progressed [40]. Given the risk of progression, we believe that it is likely that high risk patients with bronchial epithelial metaplasia and dysplasia should be followed with serial AFB, in a manner analogous to patients with Barrett's esophagus [41], unless mortality data should ultimately proves that this is unnecessary.

We found a remarkable relationship between the presence of premalignant lesions in the central airway and the presence of peripheral pulmonary nodules identified on SCT. This finding needs to be confirmed, but may be analogous to the observation by McWilliams, that premalignant lesions in the central airways seemed to predict the presence of peripheral adenocarcinomas [42]. In our smaller sample, the presence of central premalignant lesions did not yet reach significance as a predictor of peripheral lung cancer. The linkage between central premalignant lesions and synchronous peripheral nodules suggest the possibility of a premalignant "field

effect". Further study is needed to determine if central metaplasia and dysplasia are not merely precursors of airway cancer, but are also biomarkers of global de-differentiation and proliferation throughout the lung.

5. Conclusion

Our data suggest that the presence of multiple risk factors for lung cancer can guide the use of AFB. In high-risk patients, AFB as a part of bimodality surveillance will detect central lung cancer and premalignancy that is even missed by conventional sputum cytology. Further study is needed to determine if a bimodality surveillance strategy that incorporates both AFB and SCT can reduce lung cancer related mortality.

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