LUNG CANCER

Autofluorescence bronchoscopy for lung cancer surveillance based on risk assessment

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Background: 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) scanning 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 for the detection of malignancy and pre-malignant central airway lesions.

Methods: 402 patients registering at Roswell Park Cancer Institute were evaluated with spirometric testing, chest radiography, history and physical examination, of which 207 were deemed eligible for the study. 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 the chest radiograph, (3) chronic obstructive pulmonary disease with a forced expiratory volume in 1 s (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 underwent AFB, a low-dose SCT scan of the chest without contrast, and a sputum sample was collected for cytological examination. Bronchoscopic 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: Thirteen lung cancers (7%) were detected in the 169 subjects who have completed all three surveillance studies to date. Pre-malignant changes were common and 66% of patients had squamous metaplasia or worse. Conventional sputum cytology missed 100% of the dysplasias and 68% of the metaplasias detected by AFB, and failed to detect any cases of carcinoma or carcinoma-in-situ in this patient cohort. Sputum cytology exhibited 33% sensitivity and 64% specificity for the presence of metaplasia. Seven of 13 lung cancers (58%) were stage Ia or less, including three patients with squamous cell carcinoma. Patients with peripheral pulmonary nodules identified by SCT scanning of the chest were 3.16 times more likely to exhibit pre-malignant changes on AFB ($p<0.001$).

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

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 pre-invasive 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 randomised 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.[7] A subsequent non-randomised multicentre trial compared AFB with WLB in 173 patients at nine institutions[8] and found that AFB plus WLB was twice as sensitive in the detection of carcinoma-in-situ or severe dysplasia than WLB alone. These findings have been supported by numerous authors.[9–12] A recent large European randomised controlled multicentre trial[13] confirmed that WLB plus AFB was clearly superior to WLB alone for the detection of pre-neoplastic lesions.

Even though autofluorescence imaging improves the ability of the bronchoscopist to detect pre-neoplastic 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] but we reasoned that certain

Abbreviations: AFB, autofluorescence bronchoscopy; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SCT spiral computed tomography, ; WLB, white light bronchoscopy

high-risk individuals might be likely to have early central lung cancer or pre-malignancy, 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 pre-malignant lesions (metaplasia, dysplasia and carcinoma-in-situ) and (2) AFB plus SCT would be equivalent to SCT alone for the detection of lung cancer in high-risk patients.

METHODS

Patient population and recruitment

The High Risk Screening Cohort at Roswell Park Cancer Institute (RPCI) was established in 1998. This surveillance initiative incorporates an epidemiological 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 >2 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) are referred by pulmonologists and primary care physicians in the community for evaluation in the lung cancer surveillance programme. Initial chest radiographs were reviewed by the physician at the time of enrolment (GL) and were not reviewed by a B reader. The outreach effort associated with this prevention and surveillance programme has included public speaking, press releases, media interviews and the production of a colour brochure that is distributed to local pulmonary and oncology offices in the community.

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 examination. In addition, each completed a detailed epidemiological questionnaire and donated blood, buccal cell and induced sputum samples. The questionnaire collected detailed information on subject demographic data, 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 (Phillips Medical Systems NA, Bothel, Washington, USA) chest radiograph was performed to document the presence of asbestos-related lung disease. Spirometric tests were performed in the initial clinic visit with a hand-held pneumotach spirometer (Easyone Diagnostic Spirometer, Medical Technologies, Chelmsford, Massachusetts, USA). Subjects were asked to perform at least three acceptable forced vital capacity (FVC) manoeuvres and at least two efforts were required to demonstrate reproducibility within 200 ml according to the American Thoracic Society (ATS) standards. The manoeuvre 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 *et al*.[17]

Patient eligibility

In order to be eligible for the surveillance programme, patients must have demonstrated at least two 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 >2 years; (3) a cigarette smoking history of ⩾20 pack years in intensity; and (4) COPD with a documented FEV_1 <70% of predicted. Patients must also have 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 treatment for lung cancer, including video-assisted thoracic surgery, radiotherapy and/or endobronchial therapy including photodynamic therapy. Patients who were found to be eligible for the study provided their informed consent and were offered enrolment into this prospective surveillance trial which was approved by the RPCI Institutional Review Board.

Sputum cytology

Initially, patients were asked to collect early morning samples of sputum for three consecutive mornings, just before their return visit to the clinic. Spontaneous pooled sputum was obtained in the first 40 patients. Because a high proportion of these samples were classified as insufficient for cytology, the protocol was changed to require sputum induction using hypertonic saline even if a productive cough was present. Before sputum induction, spirometric assessments were performed to provide a baseline quantitative measure of lung function and for safety monitoring during sputum induction. Sputum was obtained from the remaining subjects by tidal inhalation of hypertonic (3%, 4%, 5%) saline at 7 minute intervals by ultrasonic nebuliser. If the baseline FEV_1 was <1.0 litre, only isotonic saline (0.9%) was administered. Sputum samples were stored at 4℃ until processing, for a period that did not exceed 2 h. Sputum samples were treated with Sputolysin (Behring Diagnostics, Somerville, New Jersey, USA) 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.

Bronchoscopy

AFB was performed on an outpatient basis with conscious sedation and local anaesthesia by a single pulmonologist (GL) using the LIFE I system (Xillix Technologies Corp, Richmond, British Columbia, Canada). 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 appearance epithelium were taken in all patients including those with bronchial mucosa which appeared normal. Thus, an average of 3–6 biopsies were taken during the bronchoscopy procedure. Overall, the location of the biopsies was driven by the fluorescence and white light appearance and not according to predetermined sites.

Spiral CT scanning of the chest

Non-enhanced SCT scanning of the chest was performed within 1 month of chest radiography with the GE LightSpeed Plus or the LightSpeed QXi (GE Healthcare, Milwaukee, Wisconsin, USA). Images were acquired with 1.25 mm thickness slices that were available for review at the work station and were filmed at 2.5 mm slices. Clinically significant parenchymal pulmonary

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

COPD, chronic obstructive pulmonary disease.

abnormalities identified by SCT scanning were referred for contrast-enhanced CT scans of the chest consistent with accepted algorithms.[4] RPCI staff radiologists, who were blinded to current chest radiography results, interpreted all SCT results.

Statistics

We assumed that 5% of enrolled patients would exhibit endobronchial preneoplasia, and that at least 56% of disease would be detectable with either AFB or sputum cytology. We also assumed that AFB would detect all cases detected by sputum cytology and that AFB 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 with AFB.

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

Diagnostic test	No (%)
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%)

CIS, carcinoma-in-situ.

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 one patient with COPD 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 summarises the baseline characteristics of the study participants, including referral sources.

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%), with an average age of 63 years. Approximately 39% exhibited asbestos-related lung disease on chest radiography and 65% had a diagnosis of COPD. Pulmonary symptoms from underlying pulmonary conditions were common but did not correlate with the presence of cancer or pre-malignancy. Table 2 shows a summary of the results from the sputum, AFB and SCT tests.

The majority of the sputum samples classified as "adequate" were cytologically normal (67%). Conversely, AFB detected metaplasia as the worst grade lesion in 51% of the patients, while 11.5% had dysplasia and 3% had carcinoma in-situ or endobronchial cancer. Laryngeal carcinoma in situ was also identified in two patients. In addition, 52% of the chest SCT scans had 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).

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% CI 22.2% to 44.1%) with a specificity of 64% (95% CI 35.1 to 87.2%), and the detection of pre-malignancy with AFB was significantly better (McNemar's p value <0.0001).

The 13 lung cancers identified in patients as part of this surveillance study represent an overall rate of 7%. As shown in table 4, 7 of these cases (58%) proved to be diagnosed at stage 0 or 1a. In 6 out of 7 adenocarcinoma tumours a central airway pre-malignant lesion was present, and in all but 2 of the patients a central airway pre-malignancy 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% CI 1.66 to 6.41, $p = 0.001$, table 5).

DISCUSSION

We detected a 7% prevalence of lung cancer with bimodality surveillance in this cohort of high-risk patients. This figure is higher than the reported disease prevalence in SCT-based screening trials, and we attribute this in part to risk assessment. Multifactorial risk modelling has been used in 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 a greater risk for lung cancer than those with tobacco exposure

Table 3 Relationship between detection of pre-malignancy with sputum cytology vs AFB

	Pre-malignancy†		
	Sputum positive	Sputum negative	Total
Bronchoscopy positive‡	26	52*	78
Bronchoscopy negative	5	9	14
Total	31	61	92

*McNemar's significance (p=0.000).
†Squamous metaplasia, dysplasia, or carcinoma-in-situ (distinguished by histopathology).
‡Suspicious appearance on fluorescence, prompting biopsy.

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 pre-malignant and malignant events.

Although a trend towards increased detection was observed (p = 0.20) when AFB was 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 chest radiography results,[22] central squamous cell cancers are not usually detected with this method. Henschke[4] also reported on the use of SCT scanning in a prevalence study of 1000 high-risk volunteers in which 27 cases of early stage lung cancer were detected. Of the 27 cases of lung cancer, only 2 patients had endobronchial disease and only 1 had squamous cell carcinoma. In a more recent Mayo Clinic lung cancer screening trial that enrolled 1049 participants, only 2/40 lung cancer cases were detected with sputum cytology alone and the rest were detected with low-dose SCT.[23] Bechtel *et al* reported the use of sputum cytology combined with CT scans of the chest in 126 patients with COPD; 32% of the cancers detected had positive sputum cytology and 1 of these had a normal chest CT scan.[24] Squamous cell lung cancer represents approximately 25% of all lung cancers, 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.[26–28] However, the impact of screening with flexible sigmoidoscopy on colorectal cancer mortality remains inconclusive.[29] Although randomised controlled data are 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 early central lung cancers generally have favourable 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 used 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 detected 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 randomised NCI sponsored studies designed to evaluate the added value of sputum cytology to screening chest radiography, sputum failed to reduce the overall mortality in the screened group.[33 34] Our preliminary results from the first 169 high-risk patients undergoing surveillance SCT scanning and AFB found that certain high-risk patients can exhibit negative conventional sputum cytology and still harbour significant early malignant

Table 4 Surveillance-detected cancers detected on study

Cancer cell type	Stage	CT result	AF bronchoscopy result	Treatment	Outcome notes
Small cell	Limited disease	+	+	Chemotherapy Radiation	Initial CR, PD at 24 months
Carcinoid	0	−	+	PDT	NED 3 years
Squamous cell	0	−	+	Electrocautery	NED 28 months
Squamous cell	0	−	+	Electrocautery	Expired from MI at 24 months
Adenocarcinoma	Ia	+	−	Lobectomy	NED 26 months
Adenocarcinoma	Ia	+	−	Lobectomy	NED 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 after treatment
Squamous cell	Ia	+	−	Lobectomy Chemotherapy	Adjuvant chemotherapy 5 months after resection
Adenocarcinoma	IV	+	−	Thoracotomy	Expired 6 months
Non-small cell (neuroendocrine)	IV	+	−	Chemotherapy Radiation	Receiving treatment at 6 months

+, cancer detected; −, no cancer detected; NED, no evidence of disease; PDT, photodynamic therapy; MI, myocardial infarction.

Table 5 Association between SCT detected nodule and AFB detected pre-malignant lesion

	SCT nodule			
Pre-malignant lesion	Yes	No	OR (95% CI)	p Value
Yes	58	41	3.15 (1.66 to 6.41)	0.001
No	13	12		

or pre-malignant changes in the central airway. Our findings differ from those of the European AFB trial[13] which did not detect severe dysplasia or carcinoma-in-situ in the subset of 56 patients who 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 one 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 non-invasive technique and it is likely that investigational techniques will eventually augment the sensitivity of sputum cytology. Our data reject the null hypothesis that sputum cytology and AFB are equivalent for the detection of intraepithelial neoplasia: AFB clearly increased the detection rate of pre-malignancy ($p = 0.0000$). 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 faecal 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 that described in most trials of SCT scanning[22 36–38] and closer to the value found in a similar cohort of patients with COPD.[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 pre-malignant lesions in our high-risk cohort. We believe that the detection of pre-neoplastic lesions is clinically relevant. Breuer reported the follow up of 52 patients harbouring 134 pre-neoplastic lesions 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 oesophagus,[41] unless mortality data should ultimately prove that this is unnecessary.

We found a remarkable relationship between the presence of pre-malignant lesions in the central airway and the presence of peripheral pulmonary nodules identified on SCT scanning. This finding needs to be confirmed, but may be analogous to the observation by McWilliams *et al* that pre-malignant lesions in the central airways seemed to predict the presence of peripheral adenocarcinomas.[42] In our smaller sample, the presence of central pre-malignant lesions has not yet reached significance as a predictor of peripheral lung cancer. The linkage between central pre-malignant lesions and synchronous peripheral nodules suggests the possibility of a pre-malignant ''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.

In 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 pre-malignancy 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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