Low Prevalence of High Grade Lesions Detected with Autofluorescence Bronchoscopy in the Setting of Lung Cancer Screening in the Pan-Canadian Lung Cancer Screening Study

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Low Prevalence of High Grade Lesions Detected with Autofluorescence Bronchoscopy in the Setting of Lung Cancer Screening in the Pan-Canadian Lung Cancer Screening Study.

Autofluorescence Bronchoscopy in Lung Cancer Screening

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Conflicts of interest summary:


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**Abbreviation list:**

AF: Autofluorescence

AFB: Autofluorescence bronchoscopy

CI: Confidence Interval

CIS: Carcinoma in-situ

LDCT: Low dose computed tomography

NLST: National Lung Cancer Screening Trial

OR: Odds Ratio

R/G: red/green signal intensity

ROC AUC: Receiver Operator Characteristic Area Under the Curve

WL: White light
Abstract

**Background:** Lung cancer screening with low-dose chest tomography (LDCT) has been demonstrated to reduce lung cancer mortality. Preliminary reports suggested that up to 20% of lung cancers may be CT-occult but detectable by autofluorescence bronchoscopy (AFB). We evaluated the prevalence of CT occult invasive and high grade pre-invasive lesions in high risk participants undergoing screening for lung cancer.

**Methods:** The first 1,300 participants from 7 centers in the Pan-Canadian Early Detection of Lung Cancer Study who had 2% or greater lung cancer risk over 5 years were invited to have an AFB in addition to a LDCT. We determined the prevalence of CT and AFB abnormalities and analyzed the association between selected predictor variables and pre-invasive lesions plus invasive cancer.

**Results:** A total of 776 endobronchial biopsies were performed in 333/1,300 (25.6%) participants. Dysplastic or higher grade lesions were detected in 5.3% of the participants [n=68; mild dysplasia (n=36), moderate dysplasia (n=25), severe dysplasia (n=3), carcinoma in-situ (CIS) (n=1), carcinoma (n=4)]. Only one typical carcinoid tumor and one CIS lesion were detected by AFB alone for a rate of CT occult cancer of 0.15% [95% Confidence Interval(CI) 0.0-0.6%]. Fifty-six prevalence lung cancers were detected by LDCT (4.3%). The only independent risk factors for finding of dysplasia or CIS on AFB were smoking duration [odds ratio (95% CI)] 1.05(1.02-1.07) and FEV1% 0.99(0.98-0.99).

**Conclusions:** Addition of AFB to LDCT in a high lung cancer risk cohort detected too few CT occult cancers (0.15%) to justify its incorporation into a lung cancer screening program. (ClinicalTrials.gov number, NCT00751660.)
Introduction

Screening with low dose computed tomography (LDCT) has recently been demonstrated to reduce mortality from the leading cause of cancer death in our society - lung cancer - by 20% compared to chest x-ray. While the reduction in lung cancer mortality detected in the National Lung Cancer Screening Trial (NLST) represents a major advance to reduce the impact of this disease, additional opportunities should be investigated to further reduce lung cancer mortality by detecting and treating non-metastatic lung cancer. LDCT has higher detection rates for parenchymal lung lesions (which tend to be adenocarcinomas) as opposed to central airway lesions (more commonly squamous cell carcinomas). For example, in NLST 54.6% of the screen detected lung cancers were adenocarcinoma (including bronchioloalveolar carcinoma) and 22% were squamous cell carcinoma. However, when considering interval cancers detected after a negative screen, the proportion of adenocarcinoma and squamous cell carcinoma was reversed at 20.5% vs. 29.5% respectively suggesting a larger number of missed central lesions on screening examinations. In addition, the prevalence of adenocarcinoma lesions in NLST was higher than for clinically diagnosed lung cancer rates in the USA during a similar time period (44%) while lower for squamous cell cancers (26%). Bronchoscopic evaluation of the large airways could potentially improve the sensitivity of lung cancer screening for central lesions particularly if autofluorescence bronchoscopy (AFB) is utilized, as this modality has better sensitivity than white light (WL) bronchoscopy alone. In a lung cancer screening study including LDCT, sputum cytology and AFB in a group of 561 individuals at risk of lung cancer, 7 of 28 (25%) detected lung cancers were CT occult and only detected by AFB examination, with similar results in smaller studies. We hypothesized that AFB improves the detection of early central lung cancers potentially improving outcomes associated with lung cancer screening.

Materials and Methods

The Pan-Canadian Early Detection of Lung Cancer Study, which has been described in detail previously, enrolled current or former smokers aged between 50-75 years and with a 2% or greater lung cancer risk over 5 years using a risk-prediction model developed using Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data. Participants were recruited from 8 centers across Canada (Calgary, Halifax, Hamilton, Laval, Ottawa, St-John’s, Toronto and Vancouver) from September 2008 to December 2010. The study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer, and each centers’ institutional review board approved the study (e-appendix 1). Signed informed consent was obtained from each participant.

All participants were offered baseline and year 1 LDCT, with the first half of the recruited participants to receive AFB as an additional screening modality. Within 4 weeks of the LDCT, autofluorescence (AF) and white light (WL) bronchoscopy were performed under mild to moderate sedation and topical anesthesia. Bronchoscopy was performed in the fasting state in standard endoscopy suites. The Onco-LIFE autofluorescence bronchoscopy system (Novadaq, Mississauga, Canada) was used for all cases, paired with a compatible fiber-optic bronchoscope.
Complete airway inspection was performed using both WL and AF techniques. Any visualized abnormalities in WL or AF mode were recorded and scored on a visual scale of I-IV (Class I: Normal; Class II: Abnormal – inflammation, metaplasia, low grade dysplasia; Class III Suspicious – moderate/severe dysplasia, carcinoma in-situ (CIS) or invasive cancer; Class IV: Grossly visible cancer) and a measurement of the lesion red/green signal intensity (R/G) ratio recorded in AF mode. Bronchial biopsies were obtained with a standard flexible bronchoscopy biopsy forceps device from abnormal areas and fixed in a 10% formalin solution. Biopsy locations were recorded on a procedural paper record as well as in the dictation of the procedure. A digital video record of the bronchoscopic procedure was recorded onto DVD disc along with the participant’s anonymized study identification number, and it was sent to the central study center. Pathological interpretation was performed by clinical pathologist at participating sites. Complications were recorded in the case reports and graded as minor (self-limited symptoms or events requiring minimal or no specific treatment) or major (complication requiring escalation of care or urgent interventions such as hospitalization, arrhythmia, loss of airway reflexes) by 2 independent investigators.

All 15 operators were experienced white light bronchoscopists, and at least one bronchoscopist at each site had prior training and experience with AFB. Bronchoscopists without prior experience with AFB visited the British Columbia Cancer Agency to observe procedures or were visited by one of 2 experienced operators (SCL, AMM) for initial cases. A teaching set of cases were supplied on a CD-ROM to all bronchoscopists at the onset of the study. A sample of the initial bronchoscopic examinations performed at each center (average 15 from each site) was reviewed by an experienced external bronchoscopist (TGS) blinded to any clinical data as quality assurance. Feedback from the review was forwarded back to the bronchoscopists and reviewed as a group via teleconference.

Sample size and statistical analyses

The study was powered to test the primary hypothesis that AFB would detect 10% more lung cancers (LDCT occult cancers) than detected by LDCT alone. The study sample size calculation estimated 30 lung cancers in the 1300 individuals anticipated to receive AFB and LDCT. If AFB detected 10% lung cancer cases in additional to those that are detected by LDCT, this study would have >80% power to demonstrate that this difference is >0 with a Poisson exact 95% confidence interval (CI) of 0.02-0.29 excluding the null value of zero. Secondary study aims were to determine the prevalence of CT occult dysplasia or higher grade lesions on baseline bronchoscopy and identify factors associated with them.

Descriptive analyses of the participants’ characteristics and biopsies at baseline were performed. Independent sample t-test, Mann-Whitney U test, Kruskal-Wallis test and Fisher’s exact test were used to determine significant differences between groups for continuous and categorical variables, respectively. Two-sided p-values < 0.05 were considered to be statistically significant. We determined the prevalence of CT and AFB abnormalities and analyzed the associations between selected predictor variables and any dysplasia, CIS and invasive cancer lesions, using univariate and multivariate logistic regression models with adjustment for age, gender, smoking status, intensity (cigarette/day) and duration (in years), height, weight, FEV1 % predicted and for the clustering of data within 7
study sites using STATA version 14. [Reference group: all participants (excluding participants with dysplasia/CIS lesions/invasive cancer)]. The unit of these analyses was the individual person (the highest grade lesion per individual was included in the analyses). In addition, we evaluated the utility of the R/G ratio to predict the presence of dysplastic or greater lesions during AFB with the Receiver Operator Characteristic Area Under the Curve (ROC AUC).

Results

Among 2,537 participants enrolled in the Pan-Can study 1,300 underwent AFB in addition to LDCT in 7 centers (no participants from the St-John’s site underwent AFB as this component of the Pan-Can study was complete when recruitment was initiated at that site). Baseline characteristics of participants are shown in Table 1. Procedure length was 14.4 (+/- 16.7) minutes, and a total of 776 endobronchial biopsies were performed in 333 (25.6%) participants. There was significant variation in proportion of participants undergoing at least one biopsy across study sites (6.7% to 47.4%) (p < 0.001). No major complications were noted and 40 (3%) minor complications were recorded, consisting of self-limited symptoms or events requiring minimal or no specific treatment. Quality review of 81 early cases revealed minor deficiencies in the AFB examination in 15 (18.5%) procedures such as poorly visualized segment(s), missing R/G ratio measurement, lack of biopsy for potentially abnormal areas.

Dysplastic or higher grade lesions were detected in 69 participants (5.3%) [mild dysplasia (n=36), moderate dysplasia (n=25), severe dysplasia (n=3), CIS (n=1), carcinoma (n=4)]. Three invasive non-small cell lung carcinomas were also visualized on baseline CT examination while one CT occult typical carcinoid tumour was found only on bronchoscopy. Another case of CIS was detected by AFB alone, for a prevalence of CT occult malignancy of 2/1300 or 0.15% (95% CI 0.0 – 0.6 %). Prevalence (baseline) lung cancers were detected in 56 (4.3%) participants by LDCT.

The baseline characteristics of participants according to biopsy results are compared in Table 1. Participants with dysplastic lesions or higher were more likely to be males and with lower FEV1 % predicted. In the univariate models, significant risk factors for the presence of dysplastic (any grade) lesions or CIS/invasive cancers included: lung cancer risk index; male gender; higher height and weight; duration of smoking and lower FEV1% (Table 2). In the fully adjusted model, smoking duration [Odds Ratio (OR) (95% CI)] 1.05 (1.03-1.07) and FEV1% 0.99 (0.98-0.99) were significant independent predictors of dysplasia/CIS lesions along with a trend for male gender (p=0.07) (Table 2).

Bronchoscopic grade and R/G values for different lesion types are summarized in Table 3. There were no significant differences in the mean R/G ratio for lesions with mild dysplasia, moderate dysplasia or higher and non-dysplastic lesions (0.4, 0.4 and 0.5 respectively) and the ROC AUC of R/G ratio for any dysplastic lesions (mild to severe) was poor at 0.58 (Figure 1) and only slightly higher (0.63) when only high grade/CIS lesions were considered. R/G ratios were elevated for malignant lesions (mean 1.2). Significant differences in AF grade, but not WL grade, were noted
between non-dysplastic lesions vs. lesions with any dysplasia or higher. Nevertheless the ROC AUC for both AF and WL grade was poor (AUC (95 % CI) 0.63 (0.59-0.67) and 0.52 (0.48-0.55) respectively). The finding of lung cancer at another site at baseline or during follow up was no higher in participants with at least one grade II or III lesions vs. those without (4.5% vs. 4.7%, p = 0.96) nor in participants with at least one dysplastic lesions vs. those without (7.7% vs. 4.3%, p=0.21). The mean number of grade II or III lesions detected was similar in those that were found to have lung cancer at another site vs. those that did not (0.18 vs. 0.12, p=0.57).

**Discussion**

This study of 1,300 high-risk participants undergoing AFB in addition to LDCT for lung cancer screening failed to show a significant incremental benefit of AFB. Only one case of CIS and one CT occult carcinoid tumor were detected by bronchoscopic examination. While the procedure was safe with no incidence of major complications, this very low rate of significant findings does not appear to justify the inclusion of this technique in the setting of lung cancer screening. While as many of 5% of participants did have at least one dysplastic lesion (or higher), the majority of these were of the mild – moderate grade which are not believed to require any specific intervention or even follow-up given their low rate of progression to invasive disease.

Other reports have described significantly higher rates of high grade dysplasia or greater using AFB techniques. Rates of high grade dysplasia or CIS have been found to be as high as 18%-82% but for the most part such series have recruited small cohorts of patients in specific populations at potentially higher risk of central cancers. Specifically, AFB studies have predominantly enrolled male participants, participants with sputum atypia, airflow obstruction, or patients with prior or synchronous lung or aerodigestive cancers. While our cohort was recruited based on an elevated lung cancer risk profile (≥ 2.0% over 5 years) which materialized to an actual baseline detection rate of 4.3%, no specific predisposition to central/squamous cell carcinoma was used to select participants. Prior studies often have included moderate dysplasia and even mild dysplasia in their definition of a positive AFB test further increasing positivity rates as these lower grade lesions typically represent a large proportion of lesions identified. Including moderate dysplasia in our definition of a positive AFB examination would only have increased the diagnostic rate to 2.2% of cases, not out of keeping with the largest AFB study to date which demonstrated a 5.1% detection rate in a more enriched cohort of 589 patients with either resected lung cancer, suspicion of lung cancer, abnormal sputum cytology or evidence of COPD. As such, we believe our results represent a realistic estimate of the prevalence of central pre-malignant and CT occult malignant lesions in the central airways in a large otherwise unselected but high lung cancer risk cohort.

While we found only one CT occult lung cancer (carcinoid) in this cohort, a prior study performed at one of our study sites found 4 CT occult invasive squamous cancers on baseline AFB (4/561: 0.7%) and 3 additional cases during follow-up, in a similar screening environment. A potential contributing factor to the low rate of central lesions detected in our study may relate to a shift in the prevalence of non-small cell lung cancer subtypes from squamous cell carcinoma to adenocarcinoma. Others have also noted a decrease in prevalence of high-grade pre-
invasive lesions in more recent AFB studies\textsuperscript{22}. Not only has the proportion of squamous cancers decreased over time, it has also been suggested that more of these squamous tumors are peripheral rather than central\textsuperscript{22}. Dysplasia is a lung cancer precursor and has been reported to be a potential biomarker of lung cancer risk\textsuperscript{22}. The finding of dysplasia or AFB abnormalities have been suggested to predict the development of lung cancer elsewhere in the lungs\textsuperscript{24-27} in high risk individuals, but we could not reproduce this association in our large screening cohort due the low number of dysplastic lesions identified.

A potential limitation of our study is that AFB had not been a common clinical procedure in several of our centers prior to the initiation of the project although all were experienced WL bronchoscopists and each center had at least one bronchoscopist with prior training and experience with AFB. A teaching set of cases was also developed and less experienced bronchoscopists supported by the more experienced operators involved in the project. Video recording of the procedures with centralized review (TGS) and feedback forwarded to each center was performed after initial cases by the study coordinator. In addition, ACCP guidelines suggest that basic competency can be achieve after 20 cases, a number reached early in the study for each bronchoscopist\textsuperscript{28}. Subgroup analysis of our most experienced site performing 27\% of AFB cases for this study did demonstrate more biopsies taken per participant. Nevertheless, no additional CIS or CT occult cancers were found, and only mild to moderate dysplastic lesions appeared to be more frequent than in other centers.

Significant variability in interpretation of bronchial pre-invasive pathology has also been reported even amongst experienced pathologists\textsuperscript{29,30}, a factor that could be amplified with specimen interpretation taking place at a variety of clinical sites. Such factors have been expressed as potential explanation for low incidence of high-grade lesions in other studies as well\textsuperscript{3}. We attempted to minimize such variation with dedicated reference research pathologist at each site and the use of 20 training cases supplied to each site followed by a joint study pathologist meeting at the onset of the study.

In our study population, dysplasia or CIS lesion found with AFB were positively associated with smoking duration and negatively with FEV1\%, with a trend towards increased risk for males. Smoking cessation did not appear to reduce the risk of dysplasia. Similar associations have been noted by others and could perhaps be exploited to select a population more likely to benefit from AFB screening\textsuperscript{17,19,31}.

\textbf{Conclusions}

In summary, in view of the very low prevalence of CT occult malignancy detected by AFB potentially due to a shift in lung cancer subtypes, the application of current bronchoscopic techniques cannot be justified in a screening program.
Table 1. Characteristics of participants and biopsies at baseline.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All participants 1</th>
<th>Participants with biopsy</th>
<th>Participants without any dysplasia/CIS 2</th>
<th>Other types of lesion (n=256) 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR, range)</td>
<td>Median (IQR, range)</td>
<td>Median (IQR, range)</td>
</tr>
<tr>
<td>Age, mean (Standard Deviation (SD))</td>
<td>62.5 (5.7)</td>
<td>62.7 (5.7)</td>
<td>62.4 (5.7)</td>
<td>62.4 (5.7)</td>
</tr>
<tr>
<td>Gender (males), n (%)</td>
<td>722 (55.5)</td>
<td>46 (70.8)</td>
<td>168 (65.6)</td>
<td>676 (54.7)</td>
</tr>
<tr>
<td>Smoking, pack-years, median</td>
<td>49.5 (19.1, 4.9-52.5)</td>
<td>24.5 (9.8-9.2-67.3)</td>
<td>23.7 (9.9-5-97.7)</td>
<td>24.5 (5.5-2.0-98.0)</td>
</tr>
<tr>
<td>Ongoing smoking, n (%)</td>
<td>803 (61.8)</td>
<td>43 (66.2)</td>
<td>158 (61.7)</td>
<td>760 (61.5)</td>
</tr>
<tr>
<td>Smoking intensity, Cigarette/day</td>
<td>44.3 (5.7)</td>
<td>45.3 (6.4)</td>
<td>44.3 (5.7)</td>
<td>44.2 (5.6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6 (14.5-51.3)</td>
<td>27.2 (19.5-42.5)</td>
<td>27.4 (18.7-45.5)</td>
<td>424 (34.3)</td>
</tr>
<tr>
<td>Family history of cancer, n (%)</td>
<td>447 (34.4)</td>
<td>23 (35.4)</td>
<td>78 (30.8)</td>
<td>424 (34.3)</td>
</tr>
<tr>
<td>Risk index, median (IQR, range)</td>
<td>3.4 (2.6-2.0-38.2)</td>
<td>3.6 (3.6-2.1-38.2)</td>
<td>3.3 (2.4-2.0-14.5)</td>
<td>3.4 (2.6-2.0-34.4)</td>
</tr>
<tr>
<td>Site, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calgary</td>
<td>178 (13.7)</td>
<td>1 (1.5)</td>
<td>44 (17.2)</td>
<td>177 (14.3)</td>
</tr>
<tr>
<td>Halifax</td>
<td>141 (10.8)</td>
<td>0 (0.0)</td>
<td>25 (9.8)</td>
<td>141 (11.4)</td>
</tr>
<tr>
<td>Hamilton</td>
<td>199 (15.3)</td>
<td>3 (4.6)</td>
<td>37 (14.5)</td>
<td>196 (15.9)</td>
</tr>
<tr>
<td>Laval</td>
<td>275 (21.2)</td>
<td>2 (3.1)</td>
<td>32 (12.5)</td>
<td>273 (22.1)</td>
</tr>
<tr>
<td>Ottawa</td>
<td>75 (5.8)</td>
<td>4 (6.2)</td>
<td>1 (0.4)</td>
<td>71 (5.7)</td>
</tr>
<tr>
<td>Toronto</td>
<td>86 (6.6)</td>
<td>0 (0.0)</td>
<td>17 (6.6)</td>
<td>86 (7.0)</td>
</tr>
<tr>
<td>Vancouver</td>
<td>346 (26.6)</td>
<td>55 (84.6)</td>
<td>100 (39.5)</td>
<td>291 (23.6)</td>
</tr>
<tr>
<td>FEV1 % predicted, mean (SD)</td>
<td>82 % (19 %)</td>
<td>77 % (18 %)</td>
<td>81 % (18 %)</td>
<td>80 % (20 %)</td>
</tr>
<tr>
<td>FEV1/FVC RATIO &lt; 70, median</td>
<td>63.8 (9.9, 27.6-69.9)</td>
<td>63.8 (12.8, 39-69.6)</td>
<td>62.6 (10, 37.7-69.9)</td>
<td>63.7 (9.9, 27-69.9)</td>
</tr>
<tr>
<td>Presence of emphysema, n (%)</td>
<td>760 (58.5)</td>
<td>43 (66.2)</td>
<td>148 (57.8)</td>
<td>717 (58.1)</td>
</tr>
<tr>
<td>Presence of asthma, n (%)</td>
<td>70 (5.4)</td>
<td>5 (7.7)</td>
<td>17 (6.6)</td>
<td>65 (5.3)</td>
</tr>
<tr>
<td>Presence of obstruction, n (%)</td>
<td>650 (50.0)</td>
<td>34 (52.3)</td>
<td>138 (53.9)</td>
<td>616 (49.9)</td>
</tr>
<tr>
<td>Lung cancer diagnosis at baseline CT</td>
<td>56 (4.3)</td>
<td>5 (7.8)</td>
<td>10 (3.9)</td>
<td>51 (4.1)</td>
</tr>
</tbody>
</table>

1- Participants with no biopsy n=967.
2- Mild dysplasia (n=36), moderate dysplasia (n=25), severe dysplasia (n=3), and carcinoma in situ (CIS) (n=1).
3- Normal (n=93), inflammation (n=30), hyperplasia (n=50), metaplasia (n=75). 12 participants with unsatisfactory biopsy were excluded.
4- No participants from St-John’s site underwent AFB as this component of the Pan-Can study was complete when recruitment was initiated at that site.
5- Dysplasia/CIS vs. other types of lesion. P-value < 0.05, calculated by Fisher’s exact test, t-test, or Mann-Whitney U test.
6- Dysplasia/CIS vs. participants without dysplasia/CIS. P-value < 0.05, calculated by Fisher’s exact test, t-test, or Mann-Whitney U test.
Table 2. Risk factors for finding of dysplasia or carcinoma in situ (CIS) lesions on autofluorescence bronchoscopy.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds Ratio</th>
<th>Dysplasia/CIS</th>
<th>Beta Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.97-1.05)</td>
<td>0.725</td>
<td>0.008</td>
</tr>
<tr>
<td>Gender (males)</td>
<td><strong>2.00 (1.53-2.63)</strong></td>
<td><strong>0.000</strong></td>
<td><strong>0.695</strong></td>
</tr>
<tr>
<td>Smoking intensity</td>
<td>1.01 (1.00-1.03)</td>
<td>0.072</td>
<td>0.015</td>
</tr>
<tr>
<td>Smoking duration</td>
<td><strong>1.03 (1.00-1.07)</strong></td>
<td><strong>0.042</strong></td>
<td><strong>0.034</strong></td>
</tr>
<tr>
<td>Ongoing smoking</td>
<td><strong>1.22 (0.88-1.69)</strong></td>
<td><strong>0.224</strong></td>
<td><strong>0.201</strong></td>
</tr>
<tr>
<td>Height</td>
<td><strong>1.03 (1.01-1.05)</strong></td>
<td><strong>0.004</strong></td>
<td><strong>0.027</strong></td>
</tr>
<tr>
<td>Weight</td>
<td><strong>1.01 (1.01-1.02)</strong></td>
<td><strong>0.000</strong></td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>Family history of cancer</td>
<td>1.05 (0.87-1.28)</td>
<td>0.595</td>
<td>0.053</td>
</tr>
<tr>
<td>Risk index, median</td>
<td><strong>1.07 (1.04-1.10)</strong></td>
<td><strong>0.000</strong></td>
<td><strong>0.064</strong></td>
</tr>
<tr>
<td>FEV1 %predicted</td>
<td><strong>0.99 (0.98-0.99)</strong></td>
<td><strong>0.000</strong></td>
<td><strong>-0.013</strong></td>
</tr>
<tr>
<td><strong>Multivariate model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.97 (0.93-1.02)</td>
<td>0.240</td>
<td><strong>-0.028</strong></td>
</tr>
<tr>
<td>Gender (males)</td>
<td>1.63 (0.96-2.76)</td>
<td>0.073</td>
<td>0.486</td>
</tr>
<tr>
<td>Smoking, intensity</td>
<td>1.01 (0.99-1.03)</td>
<td>0.169</td>
<td>0.012</td>
</tr>
<tr>
<td>Smoking duration</td>
<td><strong>1.05 (1.03-1.07)</strong></td>
<td><strong>0.000</strong></td>
<td><strong>0.049</strong></td>
</tr>
<tr>
<td>Height</td>
<td>1.00 (0.96-1.05)</td>
<td>0.836</td>
<td>0.004</td>
</tr>
<tr>
<td>Weight</td>
<td>1.00 (0.99-1.02)</td>
<td>0.460</td>
<td>0.004</td>
</tr>
<tr>
<td>FEV1 %predicted</td>
<td><strong>0.99 (0.98-0.99)</strong></td>
<td><strong>0.000</strong></td>
<td><strong>-0.011</strong></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CIS, carcinoma in-situ.

1- Univariate and multivariate logistic regression with adjustment for age, gender, smoking duration and intensity, height, weight, FEV1 (% predicted) [reference group: all participants excluding those with dysplasia/CIS lesions]. Statistically significant results are shown in **bold**.
Table 3. RG and visual grade score for each type of lesion sampled at bronchoscopy.

<table>
<thead>
<tr>
<th>Biopsies</th>
<th>N</th>
<th>R/G ratio median (IQR, range)</th>
<th>P-value</th>
<th>AF</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>P-value</th>
<th>WL</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal / inflammation / hyperplasia / metaplasia</td>
<td>619</td>
<td>0.5 (0.4, 0.1-2.5)</td>
<td>0.081</td>
<td>I</td>
<td>35 (6.3)</td>
<td>332 (59.8)</td>
<td>187 (33.7)</td>
<td>1 (0.2)</td>
<td>0.000</td>
<td></td>
<td>218 (40.0)</td>
<td>309 (56.7)</td>
<td>16 (2.9)</td>
<td>2 (0.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>75</td>
<td>0.4 (0.3, 0.1-1.3)</td>
<td></td>
<td>I</td>
<td>1 (1.4)</td>
<td>27 (38.0)</td>
<td>43 (60.6)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
<td>23 (32.4)</td>
<td>45 (63.4)</td>
<td>3 (4.2)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Moderate and severe dysplasia / CIS</td>
<td>47</td>
<td>0.4 (0.3, 0.2-1.4)</td>
<td></td>
<td>I</td>
<td>1 (2.6)</td>
<td>14 (35.9)</td>
<td>23 (59.0)</td>
<td>1 (2.6)</td>
<td></td>
<td></td>
<td>11 (28.9)</td>
<td>22 (57.9)</td>
<td>4 (10.5)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>31</td>
<td>0.5 (0.3, 0.1-1.4)</td>
<td></td>
<td>I</td>
<td>5 (17.9)</td>
<td>13 (46.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (20.7)</td>
<td>21 (72.4)</td>
<td>2 (6.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

P-value < 0.05, calculated by 1- Kruskal Wallis test, or 2- Fisher exact test. In the p-value calculations unsatisfactory biopsies were excluded.

AF: Autofluorescence. WL: White light. Class I: Normal, Class II: Abnormal (e.g. Inflammation, metaplasia, and dysplasia), Class III: Suspicious (CIS or invasive cancer), Class IV: Grossly visible cancer. IQR: Inter-quartile range. CIS: Carcinoma in-situ.
Figure 1. Receiver operator characteristic curve (ROC) of the R/G ratio for any dysplasia and CIS.
Reference List


Acknowledgments

AT takes responsibility for (is the guarantor of) the content of the manuscript, including the data and analysis.

AT, SCL, MCT, NT and SAK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects as well as the final version of the manuscript. AT, AMC, PM, DS, KS, SP, KY, KA, SM, SCL performed autofluorescence bronchoscopy and biopsies. AMC, PM, KS, SP, KY, KA, GN, SM, FL, MJ, MT, DI, SU, DH, JCC, HSS, CC, ZX and TGS contributed substantially to the study design, data interpretation, and review of the manuscript.

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