Close surveillance with long-term follow-up of subjects with pre-invasive endobronchial lesions

Robert AA van Boerdonk*
Illaa Smesseim*
Daniëlle AM Heideman
Veerle MH Coupé
Darryl Tio
Katrien Grünberg
Erik Thunnissen
Peter JF Snijders
Pieter E Postmus
Egbert F Smit
Johannes MA Daniels
Thomas G Sutedja

*These authors contributed equally to this work
ABSTRACT

Rationale
Autofluorescence bronchoscopy (AFB) and computed tomography (CT) enable lung cancer (LC) detection at early (pre-)invasive stage. However, LC risk in individuals harboring pre-invasive endobronchial lesions is unclear.

Objectives
To assess LC incidence and identify potential risk determinants in individuals harboring pre-invasive lesions.

Methods
In our tertiary care referral center, 164 individuals with pre-invasive lesions were monitored up to 12.5 years by repeated AFB and CT. Occurrence of LC was monitored. Clinical management depended on histological grade, with cancer patients receiving standard of care. Potential risk determinants (smoking status, baseline histology, cancer history and COPD-status) were evaluated in relation to cancer occurrence, event-free survival (EFS), and overall survival (OS).

Measurements and Main Results
During surveillance (median of 30 months, range 4-152) of 164 individuals with pre-invasive lesions (80 high-grade and 84 low-grade at inclusion), 61 LCs were detected in 55 individuals (median time-to-event 16.5 months). Twenty-three LCs (38%) were detected by CT, thirty-eight (62%) by AFB. More cancers (36/61; 59%) developed from separate, rather than initial lesional sites. Individuals with high-grade lesions were more likely to be diagnosed with LC at the same or another site in the lungs than those with low-grade lesions (p=0.03). Independent risk determinants for OS were previous curatively treated cancer and COPD (p≤0.05).

Conclusions
Presence of pre-invasive lesions, especially high-grade lesions, may serve as LC risk marker. LCs occur both at pre-invasive lesion sites and elsewhere in the bronchial epithelium or lung parenchyma. Prospective validation of biomarkers and randomized intervention studies are required to determine optimal management strategies.

INTRODUCTION

Lung cancer (LC) is the most common cause of cancer-related death worldwide\(^1,2\). The reason for the unsatisfactory overall 5-year survival rate of approximately 15% mainly lies in the often advanced stage of the disease at time of diagnosis and the inability to cure metastatic disease. Cancer screening aims at detecting cancer at an earlier stage when patients are still eligible for treatment with curative intent. The National Lung Screening Trial (NLST) has shown that screening for early parenchymal lesions in the lungs with low-dose computed tomography (LDCT) may reduce LC mortality by 20% among high-risk individuals\(^3\).

About 85% of LCs are non-small cell lung cancer (NSCLC), with adenocarcinoma being the predominant subtype that typically occurs in the lung parenchyma. Squamous cell lung cancers (SQCC) account for 20-30% of LCs\(^4\) and are regarded as central airway tumors. More recently, a shift towards more peripherally located SQCCs has been observed in surgical series (22-53%)\(^5,6\). However, a conservative estimate projects 15-20% of all LCs to be of the central type SQCC (C-SQCC), which constitutes a major worldwide cancer burden. Because early C-SQCCs are initially confined to the epithelial lining of the bronchial wall, LDCT is not the appropriate modality for early detection of such lesions. The classic method for early detection of C-SQCC is sputum cytology. This method however suffers from sampling errors, low sensitivity, technical difficulties in the preparation of samples and significant variations in intra- and inter-observer agreement\(^7\). The introduction of white light flexible fiberoptic bronchoscopy (WLB) has enabled visual inspection of the central airways. However, regardless of technological improvements that have led to the modern day videobronchoscopy systems, the sensitivity of WLB for detecting early-stage LC remains low\(^8,9\). Autofluorescence bronchoscopy (AFB) uses the spectral differences in fluorescence and absorption properties of normal and dysplastic bronchial epithelium and has markedly enabled earlier detection of centrally located pre-invasive endobronchial squamous lesions\(^10,11\).

In our tertiary care referral center, AFB is used to localize and stage the mucosal extent of pre-invasive and early invasive lesions within the bronchial tree of individuals who were referred from other hospitals because of their perceived high risk for (second) primary LC or cancer recurrence. In the current study, we report the outcomes of 164 individuals who had one or more pre-invasive endobronchial squamous lesions at first AFB examination without radiological or clinicopathological evidence of invasive LC, and who underwent combined surveillance (up to 12.5 years) with repeated AFB and CT. Outcome parameters included LC incidence, event-free survival (EFS) and overall survival (OS) in relation to patient characteristics, with the aim of identifying potential risk determinants that may be used for optimizing clinical management of subjects with pre-invasive endobronchial squamous lesions.
METHODS

Study population
A total of 479 individuals visited VU University Medical Center (Amsterdam, The Netherlands) between November 1995 and November 2011 to undergo AFB examination because of a perceived high risk for LC based on smoking habits (i.e., more than 20 pack years), chronic obstructive pulmonary disease (COPD), signs and symptoms, and/or a history of head-and-neck squamous cell carcinoma (HNSCC) or NSCLC. Of these individuals, 225 subjects met the following study entry criteria: I) presence of one or more pre-invasive endobronchial squamous lesions at the initial AFB examination, including hyperplasia (H), squamous metaplasia (SqM), mild, moderate, and severe dysplasia (miD, moD and SD, respectively), and carcinoma in situ (CIS), as confirmed by histology; and II) no signs of invasive carcinoma based on the initial CT, AFB, and histopathological findings. For analytical purposes, we excluded all subjects (n=61) with insufficient follow-up (≤3 months), leaving a cohort of 164 subjects with pre-invasive lesions. Study approval was obtained by the Institutional Review Board.

FIGURE 1 Flowchart of study cohort. Of 479 individuals at risk for lung cancer, 225 subjects had one or more pre-invasive endobronchial squamous lesions and no invasive cancer at the initial AFB and CT examination. Of these, 61 subjects were excluded from the analysis on the basis of insufficient follow-up (≤3 months), leaving a cohort of 164 subjects with pre-invasive endobronchial squamous lesions.

Autofluorescence bronchoscopy
Autofluorescence bronchoscopy (LIFE-lung system [Xillix Technologies Corporation, Richmond, BC, Canada] or SAFE-3000 system [Pentax, Tokyo, Japan]) was performed under local anaesthesia by expert bronchoscopists (JMAD, TGS). During the initial AFB examination, all suspicious hypofluorescent areas were biopsied for histopathological examination, and carefully registered according to the segmental bronchial international nomenclature12. Subsequent AFB examinations were performed on a regular basis (on average every three to six months) and biopsies were obtained from previously identified hypofluorescent areas and from newly identified suspicious areas. For each biopsy site, separate forceps were used to prevent cross-contamination. Bronchial biopsies were formalin-fixed, paraffin-embedded (FFPE) prior to histological examination.

CT imaging and management of pulmonary nodules
High resolution CT scan of the chest was performed at baseline, and on average annually thereafter, to screen the lung parenchyma for potentially malignant lesions and in case of high-grade endobronchial squamous lesions to assess presence of extraluminal mass and lymphadenopathy. Through the years the scanning machines, scanning protocols and use of contrast varied. The most frequently used scanning protocol produced a high resolution CT scan of the chest with a slice thickness of ≤1mm13,14. Small pulmonary nodules of <8mm in size were managed in accordance with the Fleischner Society guidelines15. Nodules ≥8mm were analyzed with 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning16.

Histological examination of endobronchial biopsies
Routine histological assessment of haematoxylin & eosin (H&E)-stained FFPE tissue sections was performed in accordance to the World Health Organization/International Association for the Study of Lung Cancer (WHO/IASLC) criteria for histological classification of lung and pleural tumours16,17. Histopathological classification comprised nine classes: normal respiratory epithelium (N), inflammation/bronchitis (Infl), hyperplasia, squamous metaplasia, mild, moderate and severe dysplasias, carcinoma in situ, and invasive squamous cell carcinoma.

Clinical management
The clinical management of endobronchial squamous lesions depended on the histological grade of the lesion. Low-grade pre-invasive endobronchial lesions (H, SqM, miD, or moD) were left untreated and these subjects underwent AFB at 6-monthly intervals. Individuals with SD were followed more closely at 3- to 4-monthly intervals, and CIS lesions were treated with curative intent by using endobronchial techniques such as electrocautery, argon plasma coagulation, cryotherapy, photodynamic therapy or laser, guided by autofluorescence bronchoscopy to precisely identify the margins of the lesions18,19. Subsequently, subjects were continued into the surveillance program at 3 months follow-up and underwent bronchoscopy at 3-6-monthly intervals according to lesion grade (as indicated above). In case of (suspected) progression to...
early-stage invasive cancer (stage I and II), patients received treatment with curative intent, including surgical resection or stereotactic body radiation (SBRT), and were continued in the surveillance program thereafter. In case of progression to locally advanced or disseminated cancer (stage III and IV) subjects were withdrawn from the surveillance program.

Study endpoints
The primary outcome measure was the occurrence of invasive LC. This included: I) site-specific progression, defined as C-SQCC originating from a previously AFB-visualized endobronchial lesion12; II) interval endobronchial cancer, defined as C-SQCC at a previously non-AFB suspicious site; III) recurrence of previous LC either at a local site (lesion adjacent to a staple line, bronchial stump, or in the residual lobe), regional site (involving lymph node stations 1-14 or ipsilateral lung), or distant site (involving contralateral lung, pleura, pericardium or extra-thoracic compartment)20,21; and IV) interval parenchymal cancer, defined as parenchymal LC, either histologically proven or based on clinical suspicion which involved increase of peripheral nodule size during follow-up CT imaging, or diagnostic 18F-fluorodeoxyglucose (FDG)-uptake on positron emission tomography (PET)-CT analysis22. A secondary outcome measure was site-specific progression from any AFB-visualized lesion to CIS or invasive LC.

Statistical analysis
For analytical purposes, pre-invasive lesions were grouped into I) low-grade disease (LGD), including H, SqM, miD, and moD, and II) high-grade disease (HGD), including SD and CIS. Individuals with synchronous lesions of different grades were grouped according to the highest grade found. Differences between groups were estimated using chi-square, Fisher’s exact and independent two-sample t tests. EFS was calculated from the date of first AFB examination to the date of (first) cancer detection (time-to-event) or the date when subjects were lost to follow-up due to death or censoring. OS was calculated for all subjects from the date of first AFB examination to the date of death (time-to-event), to the date subjects were lost to follow-up or up till January 1, 2013. Survival analysis was performed using the Kaplan-Meier (KM) method. Cox proportional hazards analysis with backward-stepwise elimination of non-significant parameters (p>0.10) was performed to identify potential risk determinants and correct for dependence between determinants. For all tests, two-sided p-values below 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics v20.0 software (New York, NY, USA).

RESULTS
Baseline characteristics
A total of 164 individuals (134 male and 30 female subjects) were eligible for the current study (Figure 1). Demographic, clinical and histological variables of the subjects are shown in Table 1 and Supplementary Table 1. At baseline examination, an average of three AFB-visualized pre-invasive endobronchial squamous lesions (range 1–11) were identified per individual. LGD was found in 84 individuals and HGD in the remaining 80 subjects. A total of 72 subjects (62 male, 10 female) were previously curatively treated for early-stage NSCLC and/or HNSCC (Table 1 and Supplementary Table 1).
The distribution of LGD and HGD was similar in individuals with and without cancer history (33 LGD and 39 HGD vs. 51 LGD and 41 HGD, respectively, p=0.22).

Cancers detected during close surveillance
During the period of close surveillance (median of 30 months, range 4-152 months), individuals were monitored via repeated AFB examinations (median of 5 bronchoscopies per subject, range 2-27) complemented with CT-scans on a regular basis (median of 2 CT-scans per subject, range 0-20) (Table 1). A total of 61 LCs were detected in 55 individuals within a median time-to-event of 16.5 months (Table 2). In the majority of subjects (85%, 47/55), cancers were detected within five years of follow-up. Among detected LCs, 75% were stage I (43/61) or stage II (3/61) (Supplementary Table 3). The use of AFB resulted in detection of 35 primary LCs, twenty-five of which originated from a previously AFB-visualized endobronchial squamous lesion (site-specific progression; n=24 individuals) and ten were newly identified endobronchial lesions (interval endobronchial cancers; n=10 individuals). Of the 24 individuals with site-specific progression to invasive cancer, 14 had baseline HGD (14/80, 18%) and 10 had baseline LGD (10/84, 12%) (p=0.31). Including CIS, site-specific progression was identified in 39 individuals, 24 with baseline SD (24/80, 30%) and 15 with baseline LGD (15/84, 18%) (p=0.07). CT imaging resulted in the detection of an additional 20 primary cancers, all of which were identified as interval parenchymal cancers (n=20 individuals). Cancer recurrences were detected in 6 of 72 individuals (8%) with history of cancer, at local (n=3, detected by AFB), regional (n=1) or distant sites (n=2) (detected by CT).

Event-free survival and lung cancer risk
The cumulative risk of LC in individuals with pre-invasive endobronchial lesions was estimated to be 14% at one year, 32% at five years, and 40% at ten years. For individuals with baseline HGD, estimated probabilities for cancer occurrence at any site in the lungs were 16%, 39%, and 52% at one, five, and ten years, respectively. For LGD, estimates were 12%, 25%, and 31%, respectively (Figure 2). Multivariate Cox regression analysis showed that baseline HGD serves as an independent risk factor for EFS (Hazard ratio [95%CI] of 1.84 [1.05-3.22] (p=0.03)). No associations were found between EFS and history of early-stage NSCLC or HNSCC, COPD-status, or smoking status (Table 3).

Overall survival
Eighty-four subjects (84/164, 51.2%) deceased during follow-up. LC-related mortality was 20.1% (33 LC-related deaths). The majority of LC-related deaths was found in the group of individuals with previously diagnosed NSCLC/HNSCC (20/72, 28%) vs. individuals without cancer history (13/92, 14%). OS (median±SD) was 90.1±10.8 months. Multivariate Cox regression that controlled for additional risk factors revealed both COPD and prior early-stage NSCLC/HNSCC as independent risk determinants for OS. Associated hazard ratios [95% CI] were 2.04 [1.14-3.64] for COPD GOLD I-II vs. non-COPD (p=0.02), 2.97 [1.72-5.11] for COPD GOLD III-IV vs. non-COPD (p<0.01) and 1.54 [1.00-2.39] for a previously diagnosed NSCLC/HNSCC vs. individuals without cancer history (p=0.05) (Table 3).
FIGURE 2 Estimate of cancer occurrence. Kaplan-Meier plot showing the estimated cumulative probability of cancer occurrence over time at any site within the lungs of 164 individuals with pre-invasive endobronchial squamous lesions according to their baseline lesion grade (LGD in blue and HGD in green).

DISCUSSION

The present work demonstrates that within our tertiary referral population, individuals that harbored pre-invasive endobronchial squamous lesions, especially those with high-grade pre-invasive lesions, were at high risk for primary as well as second primary LCs, both in the endobronchial and parenchymal compartments of their lungs. Bimodality surveillance using AFB in addition to CT imaging showed a 34% LC detection rate within 10 years of follow-up. The occurrence of cancer was not related to COPD, smoking status or previous NSCLC/HNSCC diagnosis. Although the presence of HGD could not predict site-specific progression of respective lesions, individuals with baseline HGD were significantly more prone to be diagnosed with cancer at any site within the lungs than those with LGD only. COPD and prior early-stage NSCLC/HNSCC were identified as independent risk determinants for OS in this cohort.

Our longitudinal cohort study of subjects with pre-invasive endobronchial squamous lesions is characterized by the most long-term assessment of clinical outcome reported as of today. Where most previous studies focused on site-specific progression to cancer, the long follow-up and CT imaging in the current study enabled us to assess cancer occurrence in both the mucosal and parenchymal compartments. Our findings that individuals with pre-invasive central airway lesions, both HGD and LGD, are at high risk for LC is in line with previous data.
In a previous study, our group reported 26% and 39% CIS or cancer occurrence in subjects who harbored low-grade and high-grade bronchial lesions, respectively. George et al. 14, Alaa et al. 15, Ishizumi et al. 16 and Jayaprakash et al. 17 performed similar surveillance studies in at risk individuals and showed LC detection rates of 41, 16, 13, and 10% within 7, 8, 9 and 4 years of follow-up, respectively. Similarly to our study, the majority of detected cancers in these studies were early-stage LCs (Stage I-II), and the number of detected LCs was highest when AFB and CT were used as complementary techniques. In addition, the observed rate of second primary LC in our study and those of others 18, 19 was considerably higher than rates reported in previous studies of early-stage LC survivors 20, 21. This may well be explained by the alternating, less sensitive surveillance approaches used in the earlier studies and/or populational differences. Altogether, the findings suggest that bimodality surveillance (AFB + CT) might serve as an interesting approach to facilitate early detection and early intervention of primary and second primary LC in high-risk individuals. Nonetheless, as bimodality screening with repeated bronchoscopy is expensive and burdensome, further efforts are required to identify at baseline those individuals who have the highest LC risk. A potentially less expensive, and certainly less burdensome approach might be a combination of using, specifically in this subgroup, CT with adequate sampling 22 and molecular testing of sputum. A predictive biomarker test could serve as prerequisite for AFB surveillance, thereby possibly reducing the number of individuals that have to undergo AFB.

In line with our previous work and the work of others, baseline histological classification per se cannot reliably predict the course of an individual pre-invasive endobronchial squamous lesion 23, 24. Moreover, the prediction of site-specific progression by means of histological classification may be imprecise as it is subject to considerable inter- and intra-observer variation 25. Biomarkers likely hold a promising future for risk assessment of pre-invasive endobronchial squamous lesions. We recently identified and validated a DNA copy number aberration (CNA)-based classifier, including changes at 3p26.3-p11.1, 3q26.2-29, and 6p25.3-24.3, as a risk predictor for cancer in individuals presenting with endobronchial squamous metaplastic and dysplastic lesions 26. Its clinical performance, however, requires confirmation in a randomized controlled prospective trial with early intervention based on the presence of these aberrations at baseline to elucidate its effect on patient outcome. Also, the evaluation of the CNA-based classifier in sputum samples, for the purpose as discussed above, is worthwhile.

Whether early intervention by means of endobronchial treatment techniques alters the course of pre-invasive squamous lesions remains controversial. The current study, in which all CIS lesions were treated, showed a site-specific progression rate (to invasive cancer) of 18% for high-grade lesions (SD and CIS). These results are comparable to other natural history studies that included treatment of high-grade lesions with HGD progression rates of 13 to 43% 27, 28 versus studies without early intervention, which showed HGD progression rates of 17 to 25% 29, 30. Further investigations are warranted as the differences in cancer incidence between above mentioned studies might be explained by populational and institutional confounders, such as differences in risk distribution and/or follow-up duration. Besides that, none of these studies included analysis of lesions with a predictive molecular biomarker, such as the CNA-based classifier as mentioned above. Finally, no data are available as to what modality is superior for the endobronchial treatment of pre-invasive lesions. Commonly used techniques include diathermy, argon plasma coagulation (APC), cryotherapy, laser, photodynamic therapy (PDT) and intraluminal irradiation therapy or brachytherapy 14. The concepts behind these techniques vary substantially, as do their effects (e.g. penetration, selectivity) on the target tissue. Therefore, after establishing efficacy of endobronchial treatment of pre-invasive lesions, different modalities would have to be compared with regard to efficacy and safety. The observation that individuals with baseline HGD were significantly more prone to be diagnosed with cancer at any site within the lungs as compared to those with LGD only, regardless of endobronchial treatment, raises questions as to how subjects bearing these high-grade pre-invasive lesions should be managed. Alternative to localized endobronchial treatment, strategies such as chemoprevention that aim to impede cancer development by targeting oncogenic pathways, deserve future consideration.

This study has several limitations. An important aspect is referral bias. Most subjects were identified during routine bronchoscopy in the evaluation of symptoms such as hemoptysis or persistent cough, before referral to our institution. The presence of symptoms and detection by WLB differs substantially from a screening setting based on risk profiling and subsequent meticulous examination of the airway mucosa with AFB. The cancer incidence in the current study might therefore be considerably higher than in a screening setting. Also, clinical predictors of outcome might have been masked in our study by the intrinsic high prevalence of these determinants (e.g., smoking and COPD) in our selected cohort; a screening setting would allow obtaining more robust conclusions. In addition, intervention bias is noted in our study. AFB-visualized and biopsied lesions might vary in the extent of lesion excision, depending on the size of the lesion, and thereby, might affect outcome. Also, treatment of lesions was only performed in case of CIS or worse. Sampling bias was controlled for by using AFB, which allows exact delineation of lesions’ mucosal margins. Another limitation is the cohort design, which precludes conclusions about the efficacy of bronchoscopic intervention for S-5QCC precursors. Finally, even though the presented cohort of subjects with pre-invasive squamous lesions is characterized by the most long-term follow-up duration, its size and the numbers of events are relatively limited nonetheless.

In conclusion, LCs occur at high rate in a population with pre-invasive endobronchial lesions. LCs are detected both by CT and AFB, and at sites of pre-invasive lesions as well as elsewhere in the bronchial epithelium and lung parenchyma. Within this selected risk population, clinical parameters at baseline lacked the ability to predict the occurrence of cancer, but individuals with high-grade pre-invasive endobronchial lesions were more likely to develop LC at the same or another site in the lungs than those with low-grade lesions. The need for studies defining the best surveillance and/or treatment approaches is underscored by the results of this study. A challenge is to assess whether early detection and minimally invasive treatment of pre-invasive endobronchial lesions may more effectively prevent LC occurrence and improve patient outcome. This should be investigated in a randomized controlled trial, which preferably incorporates biomarkers for risk stratification.
SURVEILLANCE OF SUBJECTS WITH PRE-INVASIVE LESIONS

REFERENCES


SUPPLEMENTARY APPENDIX

SUPPLEMENTARY TABLE 1 Baseline histology per individual, stratified by WHO/IASLC categorization

<table>
<thead>
<tr>
<th>Baseline histology*</th>
<th>individuals, n</th>
<th>Cancer occurrence n individuals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia</td>
<td>4</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Squamous metaplasia</td>
<td>23</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>19</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>38</td>
<td>14 (37)</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>66</td>
<td>25 (38)</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>14</td>
<td>7 (50)</td>
</tr>
</tbody>
</table>

*) Individuals with synchronous lesions of different grades were grouped according to the highest histological grade found

SUPPLEMENTARY TABLE 2 Characteristics of previous curatively treated NSCLCs and HNSCCs

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Time since treatment in months (median, [range])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>72</td>
</tr>
<tr>
<td>NSCLC, Stage</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>28 surgery</td>
</tr>
<tr>
<td>IB</td>
<td>17 surgery</td>
</tr>
<tr>
<td>IIA</td>
<td>1 surgery</td>
</tr>
<tr>
<td>IIIB</td>
<td>13 surgery</td>
</tr>
<tr>
<td>IIIC</td>
<td>-</td>
</tr>
<tr>
<td>IVA</td>
<td>2 surgery (+ CT*)</td>
</tr>
<tr>
<td>IVC</td>
<td>-</td>
</tr>
<tr>
<td>IV</td>
<td>3 surgery</td>
</tr>
<tr>
<td>HNSCC, Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>2 surgery</td>
</tr>
<tr>
<td>III</td>
<td>2 surgery + RT</td>
</tr>
<tr>
<td>IVA</td>
<td>4 surgery + RT</td>
</tr>
<tr>
<td>IVB</td>
<td>-</td>
</tr>
<tr>
<td>IVC</td>
<td>-</td>
</tr>
</tbody>
</table>

CT, chemotherapy; HNSCC, head-and-neck squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; RT, radiation therapy
* one NSCLC stage IIIB tumor received adjuvant chemotherapy
* no information of stage in medical records available
### SUPPLEMENTARY TABLE 3 Detected lung cancers, stratified by tumor stage and detection modality

<table>
<thead>
<tr>
<th>Tumor stage</th>
<th>AFB</th>
<th>CT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>27</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>IB</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>II A</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>IIB</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III A</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>III B</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>23</td>
<td>61</td>
</tr>
</tbody>
</table>