# REVIEW ARTICLE

# Advanced bronchoscopic techniques in diagnosis and staging of lung cancer

Bojan Zaric[1], Vladimir Stojsic[1], Tatjana Sarcev[1], Goran Stojanovic[1], Vladimir Carapic[1], Branislav Perin[1], Paul Zarogoulidis[2,3], Kaid Darwiche[3], Kosmas Tsakiridis[4], Ilias Karapantzos[5], Georgios Kesisis[6], Ioanna Kougioumtzi[7], Nikolaos Katsikogiannis[7], Nikolaos Machairiotis[7], Aikaterini Stylianaki[7], Christophoros N. Foroulis[8], Konstantinos Zarogoulidis[2]

[1]Institute for Pulmonary Diseases of Vojvodina, Clinic for Thoracic Oncology, Faculty of Medicine, University of Novi Sad, Serbia; [2]Pulmonary Department-Oncology Unit, "G. Papanikolaou" General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; [3]Department of Interventional Pneumology, Ruhrlandklinik, West German Lung Center, University Hospital, University Duisburg-Essen, Essen, Germany; [4]Cardiothoracic Surgery Department, "Saint Luke" Private Hospital of Health Excellence, Panorama, Thessaloniki, Greece; [5]Ear, Nose and Throat Department, "Saint Luke" Private Hospital of Health Excellence, Panorama, Thessaloniki, Greece; [6]Medical Oncology Department, "Saint Luke" Private Hospital of Health Excellence, Panorama, Thessaloniki, Greece; [7]Surgery Department (NHS), University General Hospital of Alexandroupolis, Alexandroupolis, Greece; [8]Department of Cardiothoracic Surgery, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece

**ABSTRACT**

The role of advanced brochoscopic diagnostic techniques in detection and staging of lung cancer has steeply increased in recent years. Bronchoscopic imaging techniques became widely available and easy to use. Technical improvement led to merging in technologies making autofluorescence or narrow band imaging incorporated into one bronchoscope. New tools, such as autofluorescence imagining (AFI), narrow band imaging (NBI) or fuji intelligent chromo endoscopy (FICE), found their place in respiratory endoscopy suites. Development of endobronchial ultrasound (EBUS) improved minimally invasive mediastinal staging and diagnosis of peripheral lung lesions. Linear EBUS proven to be complementary to mediastinoscopy. This technique is now available in almost all high volume centers performing bronchoscopy. Radial EBUS with mini-probes and guiding sheaths provides accurate diagnosis of peripheral pulmonary lesions. Combining EBUS guided procedures with rapid on site cytology (ROSE) increases diagnostic yield even more. Electromagnetic navigation technology (EMN) is also widely used for diagnosis of peripheral lesions. Future development will certainly lead to new improvements in technology and creation of new sophisticated tools for research in respiratory endoscopy. Broncho-microscopy, alveoloscopy, optical coherence tomography are some of the new research techniques emerging for rapid technological development.

**KEY WORDS**

Autofluorescence bronchoscopy (AFB); endobronchial ultrasound (EBUS); interventional bronchoscopy; narrow band imagning (NBI)

## Introduction

Bronchoscopy plays an important role in the diagnosis and staging of lung cancer. Despite the advances in surgical treatment and discovery of new medications, lung cancer is still the leading cause of death from malignant diseases worldwide (1-6). Fast and accurate detection and staging are important in order to make most adequate treatment plan for patients with lung cancer.

Bronchoscopic imaging techniques, such as autofluorescence imagining (AFI) or narrow band imaging (NBI), facilitate detection of premalignant lesions and early lung cancer. This might be of key importance for research in carcinogenesis. Natural course of premalignant lesions is uncertain. There are several therapeutic options for these lesions including bronchoscopic treatment; surgery or follow up, having in mind that large number of premalignant lesions will disappear spontaneously.

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Several clinical trials are aimed at evaluation of clinical course of premalignant lesions, trying to identify clinical characteristics of lesions progressing to invasive malignancy. However, detection rate of premalignant lesions under conventional bronchoscopic evaluation is low and most often accidental. Both AFI and NBI showed supremacy in detection of premalignant lesions over conventional white light videobronchoscopy. These bronchoscopic imaging techniques could be used in everyday practice for detection of synchronous tumors, for follow up after curative surgery, evaluation of vascularisation after lung transplantation or for evaluation of tumor margins (1-6).

Linear endobronchial ultrasound (EBUS) showed to be valuable in evaluation of mediastinal lymph nodes during staging of lung cancer. Lymph node stations 2, 4, 7, 10, and 11 are easily accessible for EBUS guided transbronchial needle aspiration (TBNA). EBUS-TBNA, as a minimally invasive procedure, proven to be complementary to mediastinoscopy in staging of lung cancer. However, in order to perform adequate staging of lymph nodes in lung cancer, at least three stations must be evaluated, which is often not the case. This issue must be accounted in all future investigations of EBUS-TBNA as diagnostic procedure in mediastinal staging. EBUS guided TBNA is also very good alternative in mediastinal restaging after mediastinoscopy and neoadjuvant chemo-radiotherapy. This technique decreases risks of mediastinoscopy in restaging, providing high diagnostic accuracy. Combination of EBUS-TBNA and rapid on site cytology (ROSE) can further increase diagnostic yield of the procedure. Radial EBUS with guiding sheath and miniature ultrasound probes provides high diagnostic yield in diagnosis of peripheral pulmonary lesions. Procedural risks of radial EBUS transbronchial biopsy are reasonably lower than that of transthoracic needle aspiration. Often, radial EBUS guided biopsy provides sufficient amount of tissue suitable for extensive genetic testing required nowadays in diagnostics of lung cancer. This technique could be used for assessment of invasive depth of malignant lesions in central airways. Such assessment could be beneficial for patients who are not candidates for surgery, but could be treated with interventional pulmonology techniques. Radial EBUS can be combined with other navigational bronchoscopic procedures such as electromagnetic navigation bronchoscopy (EMN) (i·Logic™ Lung Navigation System, COVIDIEN, Mansfield, MA, USA) or LungPoint Virtual Bronchoscopic Navigation system (VBN) (Bronchus Medical Inc., Mountain View, CA, USA). Published data suggest that diagnostic yield of both radial EBUS and navigational bronchoscopy, for small peripheral pulmonary lesions, could be improved if techniques are combined (7-11).

It is no longer question are these new technologies usable in everyday practice. The question is: when, which and how will these techniques be used?

Many issues are still to be addressed: high initial price of the technology and its availability in selected high volume centers of excellence (or unavailability on large scale basis), training standards across respiratory endoscopy units, provision of sufficient data from multicentre randomized trials, reimbursement of costs, *etc.* (12).

However, in spite of many open issues, these technologies are more and more available and used in many bronchoscopic suites.
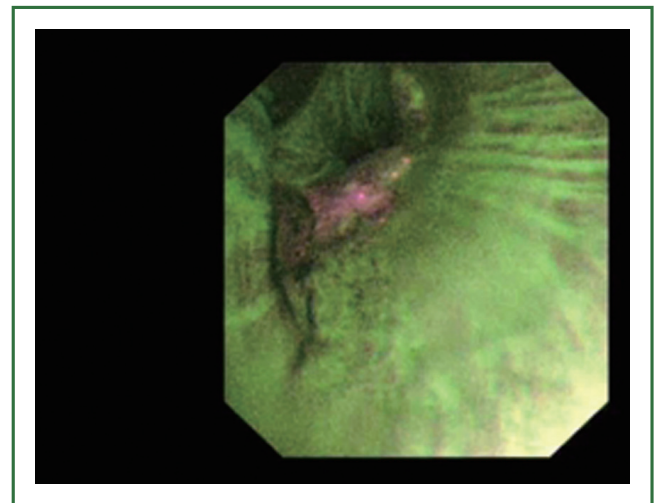
## Autofluorescence bronchoscopy (AFB)

First systems for autofluorescence examination of bronchial mucosa were robust, impractical and hardly appropriate for everyday use in diagnostic bronchoscopy. In past decade these mainly research tools became a part of everyday equipment of bronchoscopy units. New systems for autofluorescence bronchoscopy, such as Autofluorescence Imaging-AFI (Olympus Co, Tokyo, Japan), SAFE-3000 (Pentax Co, Japan), D-Light AF system (Karl Storz, Tuttlingen, Germany) and Onco-LIFE (Xillix Technologies Corp. Richmond, Canada), produce clear, high quality images of bronchial mucosa. These systems represent new generation autofluorescence videobronchoscopy devices, mainly with video-chip based videobronchoscopes. Images generated by the new systems are clear, reproducible, and easy to interpret. In the mentioned systems autofluorescence and white light videobronchoscopy are incorporated into one bronchoscope. This allows easy and convenient transition from one mode to another during endoscopic examination of bronchial tree (13-17).

The role of AFB was majorly investigated in detection of premalignant lesions of bronchial mucosa. Most of the results confirmed higher sensitivity for detection of precancerous bronchial lesions, when compared to white light bronchoscopy (WLB) alone. However, it is known that specificity of AFB for detection of premalignant lesions remains low. Reported specificity varies in different trials, one of the causes of variation could be in different systems used, but other could lay in different prevalence of lesions in investigated populations (13-17).

Specificity of AFB in follow up of surgical margins after curative surgery, detection of synchronous lesions or in evaluation of lung cancer extension specificity of AFB is significantly higher. One of the open issues on AFB is question of its usability in bronchoscopic lung cancer screening. Results of published series did not support the general use of AFB as a screening tool for lung cancer. These results suggest that AFB could be used in groups of patients at high risk for lung cancer. Some authors, however, do not recommend its use not even in high risk populations. However, AFB is more than efficient in evaluation of bronchial mucosa in certain risk groups. Patients who can benefit are: long term chronic obstructive pulmonary disease (COPD) patients, patients with prolonged cough, heavy smokers, and patients with known head and neck malignancy. In these groups indication for AFB should be made along

**Figure 1.** AFI, granulation tissue, place of prior biopsy, normal autofluorescence.



**Figure 2.** AFI, dark-violet pathological fluorescence-squamous cell lung cancer.
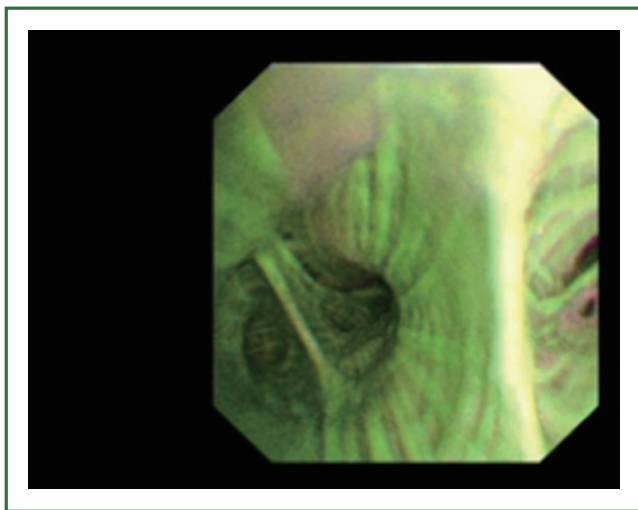


**Figure 3.** AFI, faint violet fluorescence-dysplasia grade II.

with existing indication for bronchoscopy. In recent years the indications for AFB have widened. This technique might find its place in routine bronchoscopy. It can be used for evaluation of tumor extension for follow up after surgical resection or for follow up after photodynamic therapy of centrally located early lung cancer. Sharp learning curve and clear distinction between normal and pathologically altered mucosa; make this technology acceptable for all bronchoscopists. New hardware and software improvements such as addition of backscattered light analysis, ultraviolet spectra, fluorescence-reflectance or dual digital systems could improve diagnostic yield of this technology (13-17).

### Technology overview

The cellular basis for the fluorescence phenomenon is in the

substances called fluorophores. Fluorophores are variously concentrated within tissues, showing organ typical patterns. Some of the fluorophores are tryptophane, collagen, elastine and porphyrine. Intensity of autofluorescence emission generated by the fluorophores depends on their concentration, their maximal absorption and remission and of course on the characteristics of the light source. It is believed that the concentration of the fluorophores in the pathologically altered bronchial mucosa is different than in normal bronchial mucosa (13,14). On the AFI examination normal mucosa appears green, while pathologically altered mucosa is magenta or red-brownish (Figures 1-3). Classification of endobronchial findings during autofluorescence bronchoscopy is given in Table 1.

Modern day AFB systems are based on videobronchoscopy and charged couple device (CCD) chips. One of the systems authors have more experience with is AFI by Olympus Co. (Tokyo, Japan). This system is comprised of AF videobronchoscope (BF F260), video processor unit EVIS LUCERA SPECTRUM (CV-260SL), and xenon light source CLV-260SL. The AF videobronchoscopy image could be presented on a 19 inch LCD monitor OEV-191, but it can also be produced on any other (HD) monitor. The EVIS LUCERA SPECTRUM video processor unit is based on black and white CCD chip technology, in which color separation is achieved through the use of an RGB color filter equipped with the light source unit. The AFI system utilizes high resolution imaging of the CCD chip at the distal end of the EVIS LUCERA SPECTRUM BF-F260 videobronchoscope. In addition to the blue excitation light (wavelength 390-440 nm) that causes autofluorescence, the AFI system uses green light (540-550 nm) that is mainly absorbed by hemoglobin. These two kinds of light, captured by the CCD at the tip of the bronchoscope are converted into electrical signals. The barrier filter in front of the CCD decreases excessive blue

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**Table 1.** Visual classification of endobronchial findings during autofluorescence bronchoscopy.

| Grade | AFI |
|---|---|
| Normal | Green image with normal endobronchial architecture |
| Abnormal but not suspicious | Slight decrease in fluorescence, with poorly defined margins; dark green or faint magenta image |
| Suspicious for intraepithelial neoplasia | Definite decrease in fluorescence, with clearly defined margins; magenta image; clear distortion of endobronchial architecture |
| Tumor | Visible endobronchial tumor, magenta colored |

light in order to detect the weak autofluorescence signal (13,14).

### Clinical data on AFB

Two important meta-analyses on AFB were published in last few years. Chen and associates performed a meta-analysis in order to re-examine the diagnostic efficiency of AFB compared with WLB (18). Included studies had to have definitive histology as diagnostic standard, and provided sufficient data to construct 2×2 table for assessing diagnostic yield of AFB for detection of lung cancer and premalignant lesions. Fifteen sets of data, derived from 14 studies were found to be suitable for analysis. Pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for AFB were 0.90 (95% CI: 0.84-0.93), 0.56 (95% CI: 0.45-0.66), 2.0 (range, 1.7-2.5) and 0.18 (range, 0.13-0.26), respectively. Pooled diagnostic odds ratio was found to be 11. Pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for WLB were respectively: 0.66 (95% CI: 0.58-0.73), 0.69 (95% CI: 0.57-0.79), 2.1 (1.6-2.9) and 0.50 (0.43-0.58), while diagnostic odds ratio was 4. In this meta-analysis contribution of differences in excitation light source, histological criteria and biopsy strategy was not counted as a covariate. The authors concluded that AFB was superior to conventional WLB in detecting lung cancer and preneoplastic lesions. In Sun's meta-analysis (19) the main objective was comparison between accuracy of AFB combined with WLB versus WLB alone in the diagnosis of lung cancer. The authors searched several databases in time period from January 1990 to October 2010. Twenty one studies involving 3,266 patients were ultimately analyzed in Sun's meta-analysis. The pooled relative sensitivity on a per lesion basis to detect premalignant lesions and invasive cancer was for AFB+WLB 2.04 (95% CI: 1.72-2.42) and for WLB alone 1.15 (95% CI: 1.05-1.26), and it was statistically significant (P=0.003). The pooled sensitivity on a per-lesion basis of AFB + WLB versus WLB to detect invasive cancer was 94.71% and 88.53%, respectively, while the pooled specificity on a per-lesion basis of AFB+WLB versus WLB alone was 60.94% and 79.7%, respectively. The corresponding values of relative specificity on per-lesion basis of AFB+WLB versus WLB alone was 0.65 and was statistically significant (P<0.00001). The main results of this meta-analysis showed that combination

of AFB + WLB significantly improves sensitivity in detection of premalignant lesions, even though this advantage seemed much less in detection of invasive lung cancer.

Diagnostic yield of AFB in detection of pre-malignant lesions could be highly dependent on several factors such as the type of AFB system, the grade of the lesion, incidence of lesions in investigated population and bronchoscopists experience. Sensitivity and specificity of AFB in detection of premalignant lesions in some of the largest trials is given in Table 2.

The question of low specificity remains one of the major issues of AFB. It is believed that software enhancements such as spectral analysis can improve the specificity of AFB. Several other optical enhancements were tested in clinical trial in order to reevaluate diagnostic yield of AFB. Combination of AFB with other optical bronchoscopic imaging techniques could improve diagnostic performance of AFB (35-37)

## Narrow Band Imaging (NBI)

NBI is bronchoscopic optical enhancement technology which enables thorough and detailed examination of submucosal microcapillary grid. Combination of magnification videobronchoscopy and NBI showed great potential in detection of precancerous and cancerous lesions of the bronchial mucosa. This technology enables endoscopists to obtain more detailed information on the pathologically altered mucosal and submucosal blood vessels of endoscopically accessible organs such as oro-pharynx, oesophagus, stomach, duodenal ampulla, lung, colon, bronchi and bladder. Pathological patterns of submucosal blood vessels in bronchial mucosa are known as Shibuya's descriptors (dotted, tortuous and abrupt ending blood vessels) (Figures 4-6). Most often these patterns appear together, however it is possible to determine predomination of one pattern what could be related to specific histology of lung cancer. Abnormal vascular patterns which are not pathological are known as the "background noise". These "background noise" patterns are shown on Figures 7-9. NBI could be more efficient in the detection of precancerous lesions, especially angiogenic squamous dysplasia (ASD), than the white light videobronchoscopy alone. However, this technology could be successfully used for evaluation of tumor margins, follow

**Table 2.** The sensitivities and specificities of AFB in detection of precancerous lesions.

| Author | System | Sensitivity (%) | Specificity (%) |
| --- | --- | --- | --- |
| Häußinger L. (20) | D-Light | 82.3 | 58.4 |
| Chiyo M. (21) | AFI | 80 | 83.3 |
| Chiyo M. (21) | LIFE | 96.7 | 36.6 |
| Ueno K. (22) | AFI | 94.7 | 71.1 |
| Chhajed P.N. (23) | LIFE | 96 | 23 |
| Lam B. (24) | SAFE-1000 | 91.7 | 26.4 |
| Stringer M.R. (25) | LIFE | 84.4 | 60.7 |
| Hanibuchi M (26) | SAFE-1000 | 96.8 | 56.1 |
| Beamis J.F. (27) | D-Light | 61.2 | 75.3 |
| Ernst A. (28) | D-Light | 66 | 73 |
| Herth F.J.F. (29) | AFI | 65 | 40 |
| Hirsch F.R. (30) | LIFE | 73 | 46 |
| Edell E. (31) | Onco-LIFE | 44 | 75 |
| Cetti EJ (32) | AFI | 93.3 | 81.8 |
| Zaric B (16) | AFI | 79.6 | 52 |
| Divisi D (33) | SAFE 3000 (Twin Mode) | 96 | 60 |
| Divisi D (33) | SAFE 3000 (MIX)' | 100 | 60 |
| Li Y (34) | AFI | 94.7 | 57 |
| Chen W (18) | Meta-analysis | 90 | 56 |
| Sun J (19) | Meta-analysis | 94.7 | 60.9 |
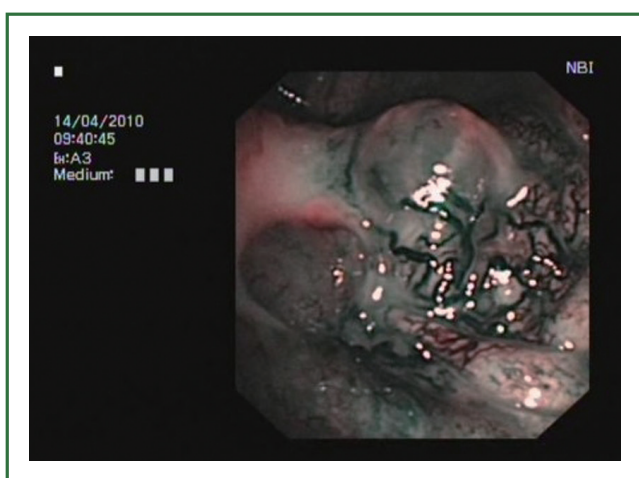


**Figure 4.** NBI, tortuous blood vessels-squamous cell lung cancer.
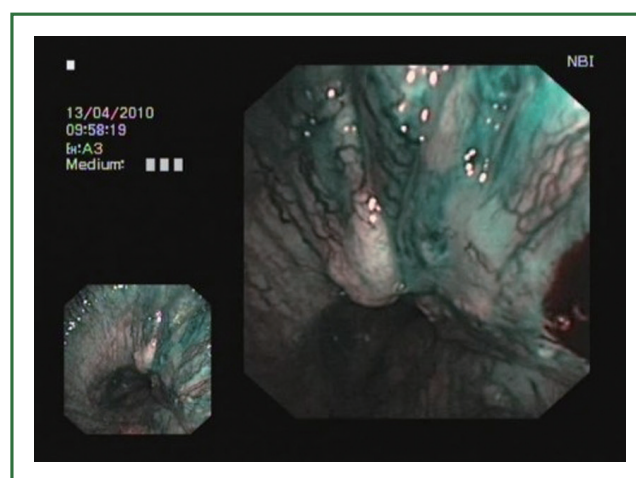


**Figure 5.** NBI, abrupt ending blood vessels-squamous cell lung cancer.

up after curative surgery or detection of synchronous tumors. The learning curve for NBI videobronchoscopy is sharp. This makes the NBI useful even when it is used by an inexperienced bronchoscopist. It is believed that the combination of NBI with autofluorescence videobronchoscopy will give better results in lung cancer detection (38-40).

NBI creates clear and sharp images of the blood vessels in the surface layers of bronchial mucosa. This technique could reveal minute patterns on mucosal membranes when the tissue is irradiated with the two narrow wave bands of light. The NBI system uses a blue narrow band, with the wave length ranging from 390-445 nm, for imaging the capillaries of the surface mucosal layer. A green narrow band (of the wave length from 530-550 nm) is used to visualize the thick blood vessels inside the membranes. This optical enhancement enables creation of clear image of the target tissue and provides a better contrast on

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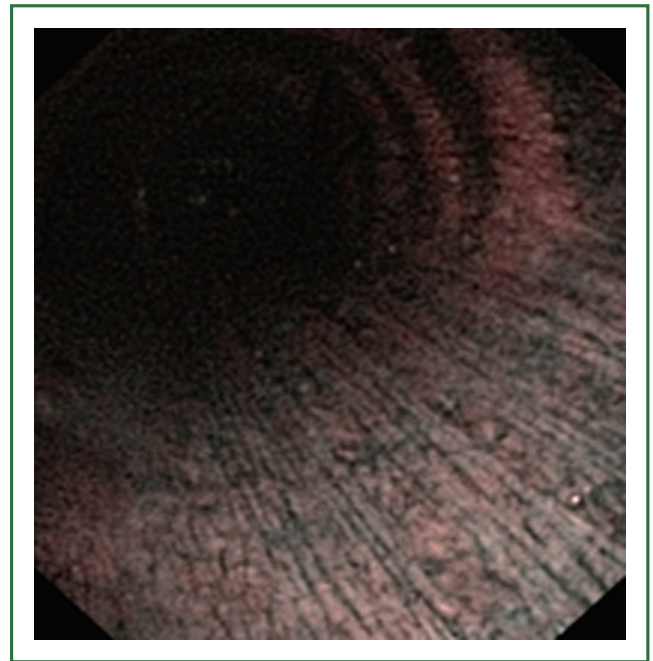*Zaric et al. Advanced bronchoscopic techniques in lung cancer*
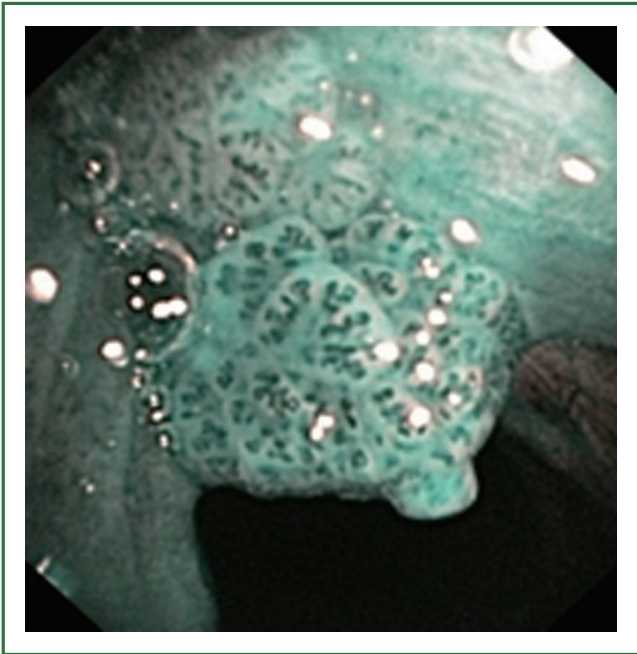
**Figure 6.** NBI, dotted vascular pattern-adenocarcinoma of the lung.
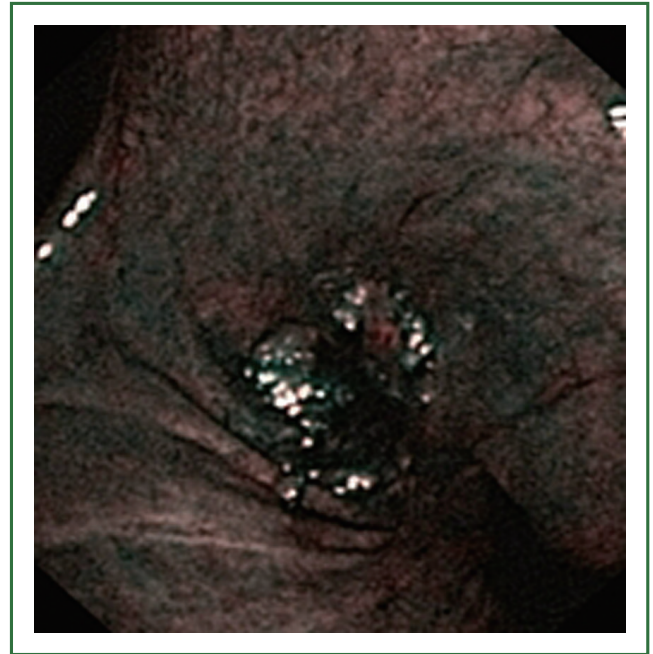


**Figure 7.** NBI, background noise-endobronchial tuberculosis.
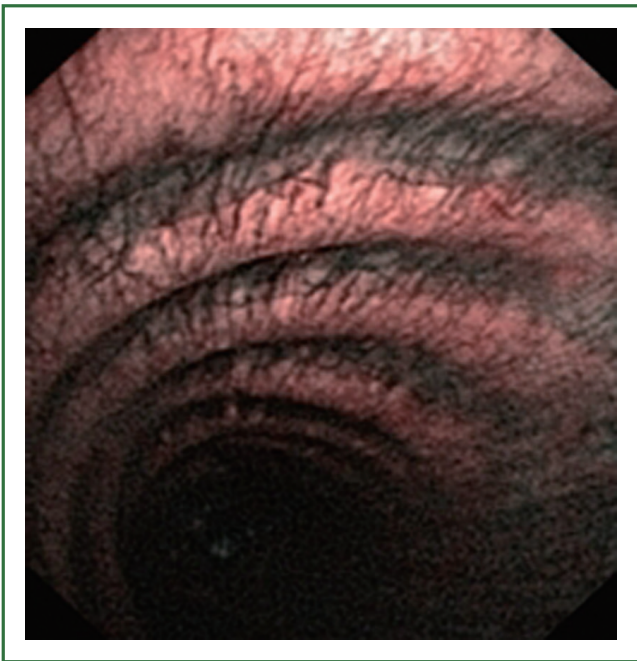


**Figure 8.** NBI, background noise-tracheitis.



**Figure 9.** NBI, background noise-chronic inflammation.

the mucosal surface, reduces examination time, and eliminates futile biopsies (38-40).

### *Technology overview*

One of the most commonly used videoendoscopy systems for NBI videobronchoscopy is based on the color CCD chip that has several tiny color filters in each pixel (EVIS EXERA II, Olympus Inc, Tokyo, Japan). However, EVIS LUCERA SPECTRUM videoendoscopy system (Olympus Inc, Tokyo, Japan) based on the black and white CCD chip, also supports NBI technology. There are brand new systems emerging on the market, such as EXERA III which also support this technique (38,39).

The EXERA II system is equipped with a digital zoom at 1.2 and 1.5 times magnification. However, the high definition endoscope (HD) possesses a physical zoom that allows the tip

of the bronchoscope to be advanced up to 2 mm away from the mucosal surface without decreasing the resolution. This combination allows 50-fold magnification. It must be underlined that these numbers are limited in reality by numerous factors affecting magnification, from the tissue characteristics, to the quality of the monitor. The combination of the high definition technology (HDTV) and NBI provides the top quality performance and the clearest images in observing the mucosal surface (39).

EVIS EXERA II system is equipped with double band filter (415 and 540 nm) which is removed from the optical axis under the normal observation. Under the NBI, the filter splits the light into two bands (415 and 540 nm) and the split light bands illuminate the mucosa. To create the color image on the monitor, the light must be outputted to R, G and B channels. In order to accomplish a high visibility of the blood vessels, the superficial capillary grid must be reproduced in the black and white pattern, and relatively thicker vessels in the deeper part of the mucosa must be highlighted with a different color pattern. The colors must be allocated according to the human visual perception. That is why the 415 nm wavelength band is allocated to B and G channels and the superficial capillary grid is visualized in the brownish color. The 540 nm band is allocated to the R channel and the deeper layer capillaries are visualized as greenish-blue or more often cyan. Bleeding is shown in the black, tar-like color, because the light rays of 415 nm and 540 nm are mainly absorbed by hemoglobin, and there is no reflected light from that surface (39,40).

### Clinical data on NBI

The study that introduced magnification bronchoscopy and NBI in respiratory medicine investigated the subepithelial patterns in bronchial dysplasia using a high magnification videobronchoscope. Sibuya *et al.* (41) developed a method of high magnification videobronchoscopy that enabled thorough visualization of subepithelial vascular patterns of the bronchial mucosa. The authors included 31 patients with sputum cytology suspected or positive for malignancy. The study protocol included the examination with conventional white light bronchoscopy, followed by autofluorescence bronchoscopy (LIFE system). Having identified the sites with pathological fluorescence, high magnification videobronchoscopy was used to examine the microvascular network at the sites of normal and abnormal fluorescence and the images were compared to the biopsy sample established pathological diagnosis. The results showed that the regular vascular patterns seen in 20/22 abnormal sites (on fluorescence bronchoscopy) were associated with bronchitis. On the other hand, the vascular networks with increased vessel growth and complex networks of tortuous capillaries observed in 15 of 21 fluorescently abnormal sites

correlated to bronchial dysplasia. There was a significant difference (P<0.0001) between bronchitis and dysplasia. The study concluded that magnification videobronchoscopy enabled differentiation between bronchitis and dysplasia.

In 2003, Shibuya *et al.* published the study that combined magnification videobronchoscopy and narrow band imaging (42). The aim of that study was to investigate the usefulness of magnification videobronchoscopy and NBI in examining ASD. The study population included heavy smokers with a high risk of lung cancer. There were 48 patients with the sputum cytology suspected or positive for a malignancy included in the study. The bronchoscopic exploration started with the white light bronchoscopy, followed by autofluorescence bronchoscopy. This study found significant correlation between the frequencies of the dotted vessels visualized by NBI and the tissues pathologically confirmed as ASD.

One of the most valuable publications on NBI videobronchoscopy was published by Herth *et al.* (43). The authors evaluated the diagnostic yields of NBI individually and in combination with WLB and AFI. The primary aim was to determine the value of NBI as compared to AFI and WLB, not to examine the value of bronchoscopy in the early lung cancer detection. The relative sensitivities of AFI and NBI when compared to WLB were 3.7 and 3.0 respectively, both were statistically significant. NBI showed significantly higher specificity when compared to AFI, but without significance for sensitivity. Combining the findings of WLB to either AFI or NBI produced no change of the relative sensitivity of any of the procedures. The relative sensitivity of the combined AFI and NBI was 4.0, but without significance when compared to AFI or NBI alone. In another words, the combination of AFI and NBI induced no significant increase of the diagnostic yield. The sequence of the techniques had no impact on the findings obtained. In the conclusion, the authors stated that detection of angiogenic squamous dysplasia by NBI technology might be advantageous over AFI screening in detection of early stage lung cancer. It was confirmed that NBI could increase specificity without compromising the sensitivity.

In several studies published by our group we investigated diagnostic efficiency of NBI in detection of tumor margins and intrabronchial extension of invasive lung cancer. In these trials NBI was not used for diagnosis of gross tumorous masses, it was used solely for investigations of tumor margins. In pilot trial we found the sensitivity, specificity, PPV and NPV of NBI for the visualization of the tumor margins to be 97.8%, 85%, 93.7% and 94.4%, respectively. The sensitivity, specificity, PPV and NPV of the white light videobronchoscopy was significantly lower, 92.3%, 60%, 69.6% and 88.9% respectively. Larger confirmatory trial followed. In the final study, the specificity, sensitivity, PPV and NPV of 85.6%, 95%, 84% and 95.6%, respectively were obtained (38,39). In one of the latest trials we investigated

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**Figure 10.** EBUS guided TBNA, real time image of the needle inside mediastinal lymph node station 4D.
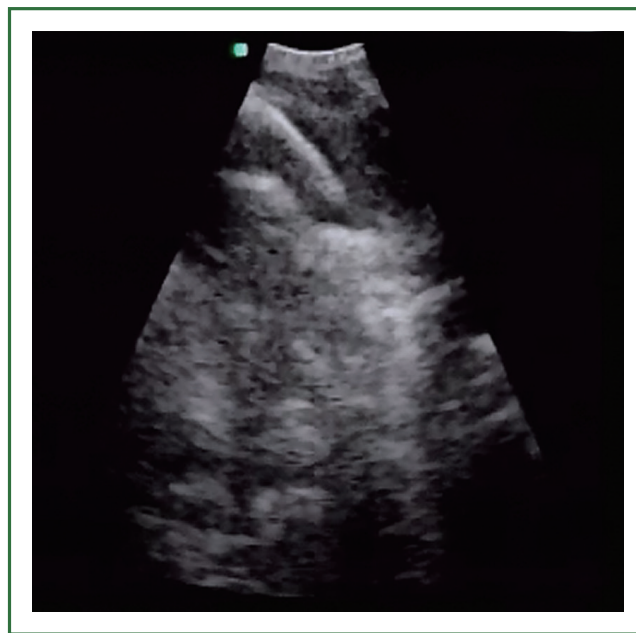


**Figure 11.** EBUS guided TBNA, real time image of the needle inside mediastinal lymph node station 4L.

relationship between vascular pattern and lung cancer histology. Dotted blood vessels were significantly (P<0.000) associated with adenocarcinoma, identified in 68.4% adenocarcinoma and 31.6% squamous cell cancers (SCC). Tortuous blood vessels were identified in 72% SCC, 8% adenocarcinoma, 12% small cell lung cancer (SCLC) and 8% of large cell lung cancer (LC). Tortuous blood vessels were significantly (P<0.000) associated with SCC. Abrupt ending vessels were identified in 81% SCC, 14.3% SCLC and 4.8% adenocarcinoma, and were significantly associated (P<0.000) with SCC. This study concluded that dotted visual pattern of blood vessels identified during NBI videobronchoscopy is highly suggest adenocarcinoma histology of lung cancer. Tortuous and abrupt ending blood vessels visualized under NBI videobronchoscopy suggest squamous cell histology of lung cancer (44).

The place of NBI in the assessment of premalignant and malignant lesions has been defined: this technology is efficient, specific and sensitive enough in the detection of early lung cancer. The NBI is sensitive and specific enough to identify dysplasia, carcinoma in situ and invasive lung cancer. It is a technology with a potential to contribute to the investigations and understanding of neo-angiogenesis as a crucial part of carcinogenesis of lung tumors. The role of NBI in the investigations of vascular anomalies in COPD and bronchial asthma is a challenging field for pulmonologists and bronchologists. It would be wise to attempt at investigating the blood vessel patterns in patients with COPD and correlating the findings to the responsiveness to therapy and rate of exacerbations. One of the emerging indications for the NBI

in respiratory endoscopy is the quantitative assessment of the airway vascularity after lung transplantation. This will be one of the major advantages NBI can offer in relation to other imaging techniques (40-45).

## Endobronchial ultrasound (EBUS)

EBUS has broadened the diagnostic potential of bronchoscopy. EBUS exists in two forms: radial and linear EBUS. Both types use a transducer that produce and receive the sound waves. A processor integrates the sound waves reflected by tissues to generate the two-dimensional ultrasound image. Radial EBUS probes facilitate not only guided TBNA and guided biopsies of peripheral lung lesions but also evaluation of airway wall structure. Linear EBUS, on the other hand, facilitates TBNA of mediastinal, hilar, and intrapulmonary lymph nodes under real-time ultrasound control with a high diagnostic yield (46-50). Linear EBUS consists of dedicated bronchoscope with US probe at the distal tip and ultrasonic center. This EBUS bronchoscope incorporates color and power Doppler, with corresponding high resolution flow modes, to allow better detection of vascular involvement before lymph node sampling. Ultrasound and the conventional bronchoscopic images can be viewed simultaneously. TBNA is performed with a specially designed needle within a catheter device, which is passed through the working channel of the bronchoscope. Figures 10 and 11 show the transbronchial needle inside the lymph node. One of the major advantages of this technique is real-time aspiration of the mediastinal lymph nodes. Depending on the diameter of
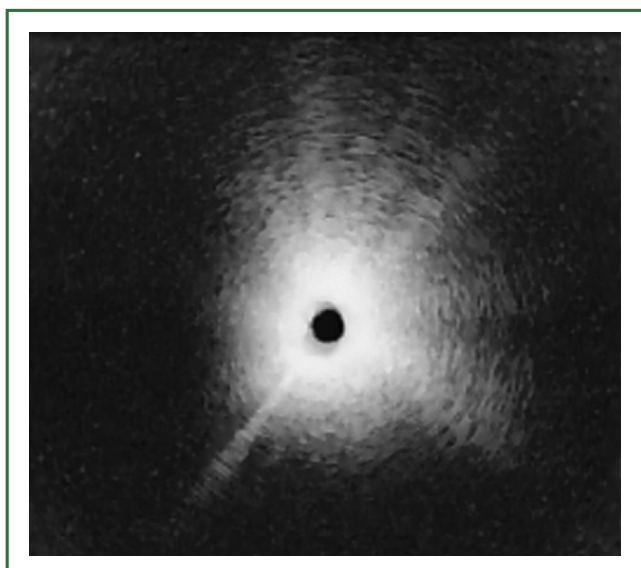
**Figure 12.** Radial EBUS, snow storm pattern of normal EBUS image in lung periphery.
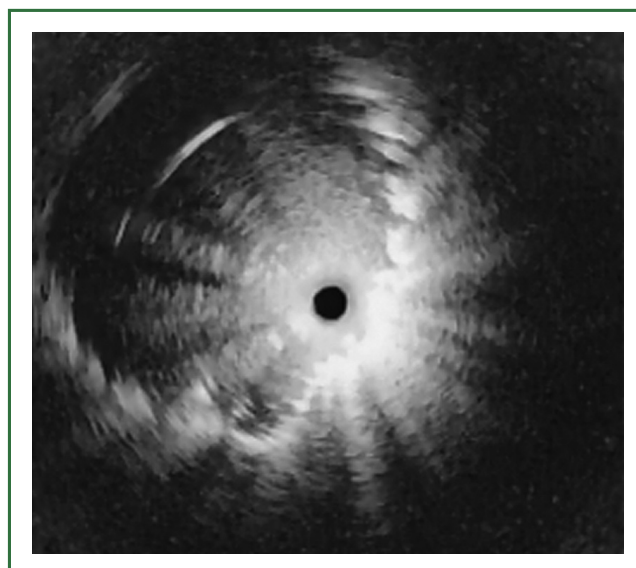


**Figure 13.** Radial EBUS, image of the peripheral pulmonary lesion.

**Table 3.** Diagnostic efficiency of EBUS.

| Author | Type of EBUS probe | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|
| Herth (53) | Linear | 94 | 100 | 100 | --- |
| Rintoul (54) | Linear | 85 | 100 | 100 | 71.4 |
| Herth (55) | Linear | 92.3 | 100 | --- | 96.3 |
| Herth (56) | Linear | 89 | 100 | --- | 98.9 |
| Szlubowski (57) | Linear | 89 | 100 | --- | 83.5 |
| Szlubowski (57) | Linear | 91.5 | 100 | | 87.6 |
| Yasufuku (58) | Linear | 81 | 100 | 100 | 91 |
| Anraku (59) | Linear | 93.1 | 100 | --- | --- |
| Tournoy (60) | Linear | 82 | --- | --- | 23 |
| Herth (61) | Linear | 76 | 100 | 100 | 20 |
| Annema (62) | Linear | 94 | --- | --- | 93 |
| Gu (63) | Radial | 93 | 100 | --- | --- |
| Steinfort (64) | Radial | 86 | --- | --- | --- |
| Steinfort (65) | Radial | 73 | 100 | --- | --- |
| Eberhardt (66) | Radial | 72 | 100 | 100 | 38 |

sampling needle, cytology or histology samples can be obtained and used for diagnosis. In recent years new sampling instruments are under development and evaluation. One of the potentially most useful will be TBNA forceps, developed by Herth *et al.*, which will allow better quality of histology samples. It has been shown that EBUS TBNA might be complementary to mediastinoscopy in staging of lung cancer. After localization of the peripheral lung lesion with the radial EBUS probe, the probe must be pulled out of the working channel of the bronchoscope.

Sampling tool (forceps) could then be introduced and placed in the lesion in order to take samples. Fluoroscopy is often used to verify the position of the forceps. Development of new smaller probes with guiding catheters solves the problem of navigation. The probe is placed into the catheter and slided through working channel of the bronchoscope. Once the place of tumor was visualized by radial EBUS probe, the probe is being removed while the catheter remains in place, sampling tool is than inserted through the catheter (Figures 12,13) (51,52) (Table 3).

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## Conclusions

Advanced bronchoscopic techniques are helpful in everyday diagnostic workup of lung cancer. Imaging technologies provided more accurate visualization of pathological alterations in bronchial mucosa, enabling more adequate assessment of endobronchial processes. On the other hand EBUS technology provides minimally invasive highly accurate evaluation of the mediastinum which might be complementary to mediastinoscopy. Radial EBUS probes are beneficial in diagnosis in peripheral lung lesions, together with rapid on site cytology, radial EBUS shows high diagnostic yield. In combination with navigational technologies that yield can be further increased.

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