

The Future of Bronchoscopy in Diagnosing, Staging and Treatment of Lung Cancer

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Key Words

Bronchoscopy · Pulmonary biopsy · Lung cancer · Pulmonary stents · Cancer staging

Abstract

Bronchoscopy is a central technique in diagnosing lung cancer, but also in different therapeutic approaches. A lot of techniques are available. The most common indication for bronchoscopy is for tissue sampling and determining the extent of lung cancer. Established diagnostic techniques are forceps biopsy, aspiration or brush cytology sampling, or needle aspiration. Laser therapy, electrocautery, cryotherapy and stenting are well-described techniques for the palliation of symptoms due to airway involvement in patients with advanced stages. Newer technologies, with an established role in clinical practice, are endobronchial ultrasound, autofluorescence bronchoscopy, and electromagnetic naviga-

tion. Other technologies, such as magnification, narrow-band imaging and confocal fluorescence microendoscopy, are in development for the use within the airways.

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Introduction

Gustav Killian [1] reported his experience with the first bronchoscopy in 1898. Technologic advances during the next century made bronchoscopy a pivotal diagnostic and therapeutic tool in pulmonary medicine. Several pulmonologists refined the technique of rigid bronchoscopy, but the advent of flexible fiber-optic bronchoscopy, pioneered by Ikeda et al. [2] in 1967, opened new horizons to clinicians. At the end of the 1980s, videobronchoscopy was developed, which greatly improved imaging quality and electronic data storage. Thereafter, other bronchoscopic applications, such as endobronchial ultrasound and autofluorescence bronchoscopy [3, 4], were introduced. Surprisingly, the 'historic' rigid bronchoscope also adapted extremely well to the introduction of modern therapeutic tools, such as laser, cryotherapy, electrocautery, and stents, resulting in the endoscopic subspecialty of interventional bronchoscopy [5].

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We give an update on the current state-of-the-art techniques in diagnostic and therapeutic bronchoscopy, review some recent developments in the technology, and note some promising techniques on the horizon.

Current Techniques in Diagnostic Bronchoscopy

Various diagnostic accessories can be inserted through the working channel of the flexible bronchoscope. These accessories include biopsy forceps, needles, and brushes, and they have greatly aided in the diagnosis and staging of lung cancers. Their combined effect has greatly improved the ability to obtain pulmonary biopsies, especially of ever smaller lesions. Computed tomography (CT) is today one of the cornerstones of imaging techniques [6].

Forceps Biopsy

Visualizing lesions through a bronchoscope is usually not sufficient to determine a precise diagnosis or to guide patient management. Confirmation of the pathological diagnosis through biopsy is required. A variety of instruments with improved distal control have been developed to permit tissue cutting and retrieval of biopsy specimens.

The cutting cups of biopsy forceps may be round or elliptical and may have smooth or jagged edges. Non-serrated edges, however, seem to reduce tissue trauma and the concomitant risk of bleeding. The biopsy procedure is simple and generally associated with only minimal complications in the case of a visible lesion. Even peripheral lesions, which are not visible through the bronchoscope, can be biopsied [7]. With diffuse parenchymal or interstitial lung disease, specimens may be obtained without fluoroscopic guidance [8]. With smaller or focal lesions, however, the biopsy success rate increases with fluoroscopy. The success rate ranges from 30 to 70%, depending on the size and location of the lesion [9, 10].

Transbronchial Needle Aspiration

The first to pass a transbronchial needle through a rigid bronchoscope was Schieppati [11]. Wang et al. [12] then developed a flexible needle technique, using a fiber-optic bronchoscope. Initially, needles were designed to obtain cytologic material. Subsequently, they were designed to obtain histologic specimens from submucosal lesions and peribronchial mediastinal and hilar lymph nodes (fig. 1). These needles are useful in obtaining biopsy specimens from areas that cannot be sampled with simple bronchoscopy forceps or brushes. The main indication for needle aspiration is staging of lung carcinoma [13].

The working channel of the scope may be perforated if the needle is advanced with the tip exposed, so the tip of the needle is protected by a metal hub during insertion and withdrawal. The success of the needle aspiration biopsy depends on optimizing the bend of the tip of the bronchoscope and on properly approaching the bronchial wall. Depending on the diseases, the biopsy success rate leading to a diagnosis ranges up to 80% for peribronchial lesions [14].

Brushing and Aspiration Cytology

Bronchial washings are the secretions aspirated back through the bronchoscope channel after instillation of saline into a major airway. The secretions obtained by this method do not represent material from the bronchiolar or alveolar level. Moreover, they may be contaminated by upper airway secretions. Therefore, bronchial washings are not appropriate specimens for bacterial culture, but they can be of help to diagnose centrally located lung cancer by detection of exfoliated malignant cells or for diagnosing pneumonia caused by strictly pathogenic organisms, such as *Mycobacterium tuberculosis* and endemic systemic fungi, particularly in patients for whom the bronchioloalveolar lavage (BAL) return volume is inadequate [15].

Routine bronchial brushes are designed for exfoliative cytologic diagnosis of malignancies. In comparison to the protected brush used to harvest infectious organisms, the cytology brush is stiffer in order to obtain cellular material from the airway wall. The incidence of mucosal haemorrhage is therefore slightly higher after this procedure.

Because the usual bronchial brush is not protected from contamination during passage through the bronchoscope channel, it is inappropriate for bacterial cultures. In contrast, because cells are obtained from the airway walls, specimens from a cytology brush are appropriate and accurate for the diagnosis of the cytopathologic changes associated with cancer or viral inclusion bodies in airway cells [15].

The diagnostic yield for washing in patients with endoscopically visible (central) tumours varies from 49 to 76% and is similar to the yield for brushings (52–77%) but is inferior to the yield of biopsies (71–91%). The diagnostic yield of washings in patients with endoscopically non-visible (peripheral) tumours varies from 35 to 52% and is similar to the yield for brushings (26–52%) [16, 17].

More recently, this technique has also been used to obtain specimens for molecular analysis. Zochbauer-

Muller et al. [18] examined aberrant methylation as an important method for silencing tumour suppressor genes in cancers. In lung cancer, methylation of the genes retinoic acid receptor- β_2 (RAR- β_2), CDH13 (H-cadherin), p16(INK4a) (p16), RASSF1A (RAS association domain family I) is frequent. Thus, they investigated methylation of these genes in four different types of specimens (oropharyngeal brushes, sputum samples, bronchial brushes and BAL samples) of the upper aerodigestive tract epithelium from heavy smokers without evidence of cancer but with morphometric evidence of sputum atypia and compared the frequencies of methylation in the different types of specimens. The group could demonstrate that methylation occurred more frequently in samples from the central airways (bronchial brushes) compared to BAL. The value of the results must be explored in additional tests, bronchial brushes seem the ideal tool for sampling the material [18].

Current Techniques in Therapeutic Bronchoscopy

Interventional bronchoscopy has now come of age [19, 20]. A variety of interventional bronchoscopic techniques combined with surgery, external beam radiation, or chemotherapy form the cornerstone of treatment for endobronchial malignancies. Recent advances in this field allow effective palliation of many, if not most, endobronchial tumours by ameliorating obstructive and haemorrhagic complications. These benefits are all the more important considering that about 300,000 new cases of lung cancer are diagnosed in Europe each year, and tumours in the majority of these cases are unresectable. A substantial number of patients with lung cancer require therapy for symptomatic airway lesions. In addition, quite some patients with non-pulmonary tumours have endobronchial metastases that are potentially amenable to multimodality therapy [21].

Complications may arise when a patient with an intrathoracic malignancy and endobronchial involvement undergoes conventional treatment. External beam radiotherapy or chemotherapy can exacerbate endobronchial inflammation, produce swelling, and induce airway necrosis. These effects may compromise airway lumen diameter, leading to distal lung collapse and post-obstructive pneumonia [16, 22]. A multimodality treatment approach to lung malignancies can potentially avoid, alleviate, or reduce these complications [23].

Laser Therapy

Common endobronchial lesions include malignant and benign pulmonary tumours. Although removal with simple biopsy forceps or debulking with the edge of the rigid bronchoscope have been described, these procedures are fraught with risks, including fatal bleeding. Laser technology has provided a new therapeutic tool.

The first laser used to treat tracheobronchial lesions was the CO₂ laser. Because of its far infrared spectrum (wavelength 10,600 nm), this beam can be transmitted safely only with special mirror systems and a rigid bronchoscope. The value of the CO₂ laser is its ability to cut and vaporize tissue with a high-energy beam. The development of lasers with different wavelengths and, in particular, of neodymium-doped crystal lasers, has permitted transmission of the beam through fiber-optic systems [24].

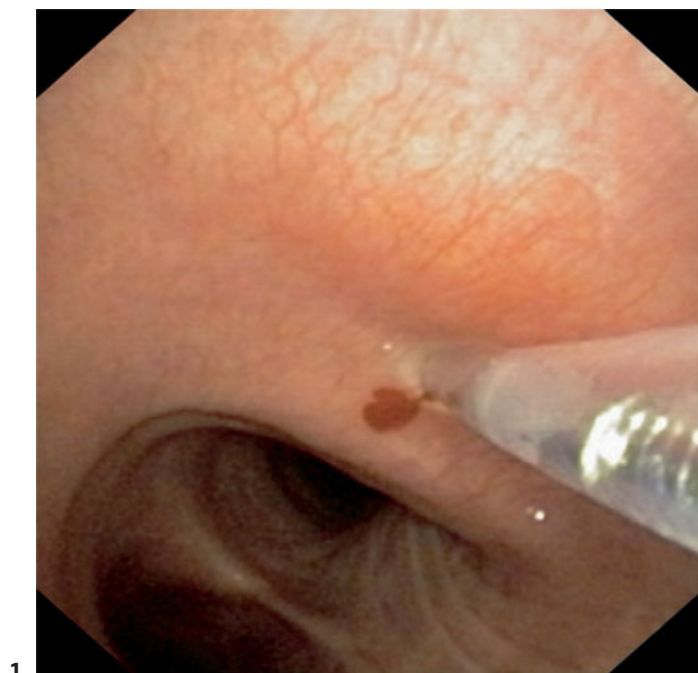
The neodymium-YAG laser has a wavelength of 1,064 nm, which is in the near-infrared spectrum. Its high scattering coefficient in soft tissue allows it to penetrate deeply. It also has a strong thermal characteristic that can be used to coagulate blood vessels and other viable tissues when placed at a distance from the target. Using a contact technique with specially designed sculpted or sapphire tips, the neodymium-YAG laser can be used bronchoscopically to coagulate bleeding sources and to prepare a tumour before mechanical debulking [25].

Many reports have documented the beneficial effects of endobronchial neodymium-YAG laser therapy, particularly in patients whose large airways are obstructed by primary thoracic or metastatic malignant tumours [26, 27]. Treatment success rate is based on the appropriate selection of patients, as well as on the experience and training of the endoscopist.

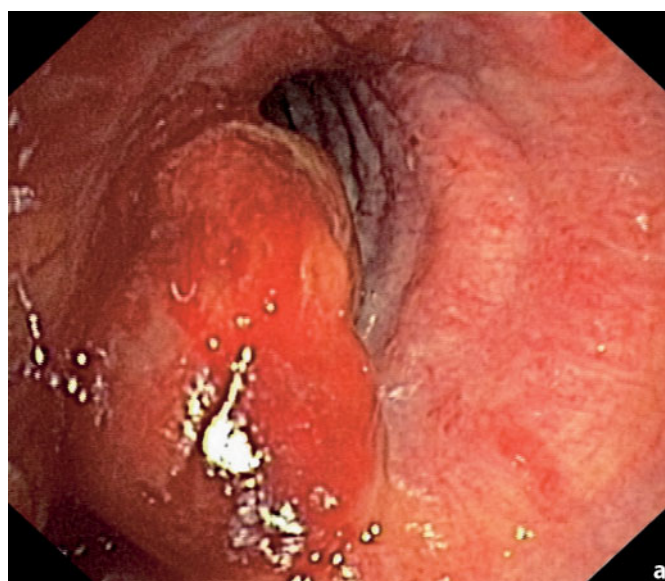
Electrocautery and Cryotherapy

Other techniques of tissue destruction can be applied through the bronchoscope. Electrocautery has been used effectively in gastrointestinal endoscopy. Tissue is destroyed by intense coagulation and vaporization [28]. The depth of penetration and resulting injury are, however, much more difficult to control than with laser cautery. On the other hand, a bronchoscope had to be specially designed to prevent short circuits and potential injury to both the patient and endoscopist: an electric spark in an oxygen-enriched environment may result in combustion and severe burns. However, this technique is less expensive than laser therapy [29].

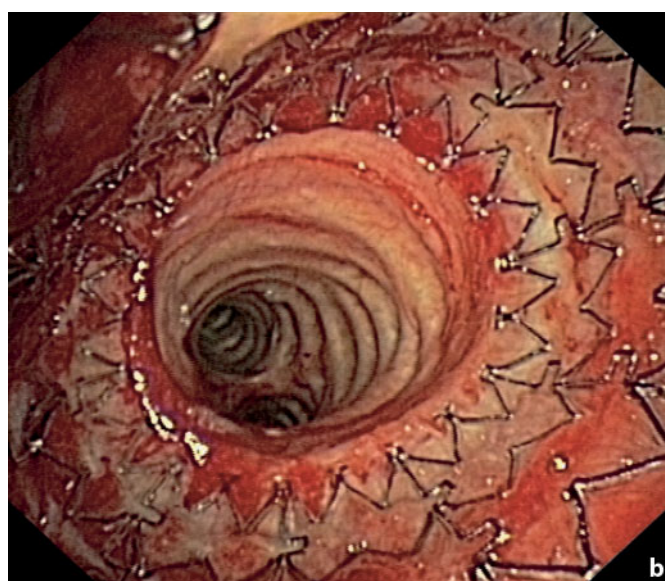
Cryotherapy is associated with even greater difficulties in control and depth of penetration [30]. Special probes are



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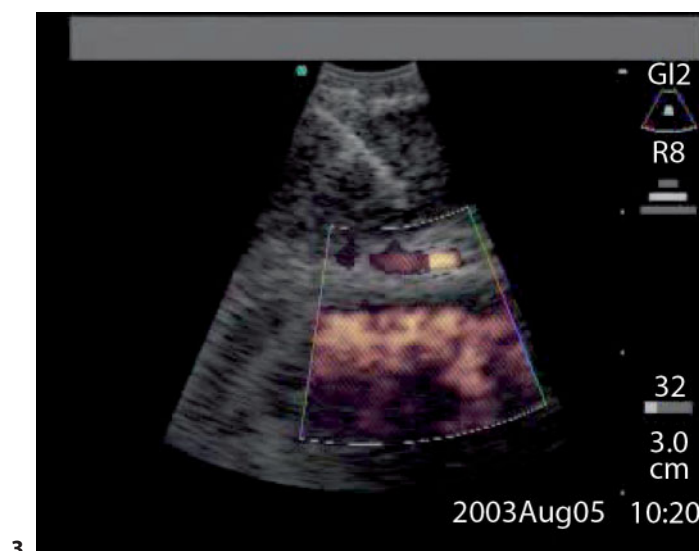


a



b

2



3

Fig. 1. TBNA of the lymph node position 4r.

Fig. 2. a Exophytic tumour in the trachea before recanalization. **b** Result after laser therapy and stent placement.

Fig. 3. EBUS-TBNA of an enlarged lymph node. The position of the vessel is checked by the power Doppler mode, the needle is seen in the node.

inserted through the bronchoscope until they touch the target tissue. Through a channel in the probe, liquid nitrous oxide or liquid nitrogen is introduced, resulting in the rapid creation of an 'ice ball' (about -20°C) at the tip of the probe. The tissue is exposed for about 20 s and then thawed and removed. Inappropriate manipulation, exces-

sively rapid thawing, or premature detachment of the probe may result in bleeding or tissue fracture. Cryotherapy is inappropriate for patients requiring rapid reopening of the airways because its beneficial effects are achieved only after subsequent removal of the sloughed necrotic tissue. Cryotherapy is also less effective in treating tissues with

poorly cellular regions or those with limited vascularization, such as benign fibrotic structures and lipomas [31].

Stenting

Most bronchial stents have had disappointing long-term results. Initially, they were rigid devices made of rubber, metal, plastic, or composite materials. More recently, however, stents made of silicone or special alloys, such as nitinol (a nickel-titanium alloy with shape and size memory capacity), have had good results [32].

Bronchial stents should be placed according to three basic principles: safe placement and fixation of the stent, safe ventilation during the procedure, and safe handling of potential complications. The ideal indication for stent placement is a short segment of stenosis (in two or three cartilaginous rings) in the left main-stem bronchus or the trachea, preferably secondary to compressible extrinsic compression or exophytic tumour growth. The stent should prevent airway collapse, maintain airway integrity, and allow acceptable airflow. Stents should be considered only as mechanical palliation, however, not as a cure for the underlying disease [33].

The most popular tracheobronchial stents were developed in France by Dumon and colleagues [34]. These stents are of various lengths and diameters and are made of silicone. They have special retention protrusions or studs on their external wall, which help stabilize the stent in the bronchus. Placing the stents requires special training and dexterity because placement must be accomplished without direct visualization and with some risk to ventilation. The advantage of these stents, however, is their ease of removal in case of complications. The most frequently reported complications are stent migration and overgrowth at the edge of the prosthesis by tumour or granulation tissue [34].

Another recently developed one is the so-called 'dynamic stent.' This stent is particularly well suited for managing lower tracheal, carinal, and main-stem bronchial stenosis [35]. The stent is constructed from silicone and a horseshoe-shaped metallic 'scaffold,' which mimics the cartilaginous rings. The stent has a soft posterior wall, similar to that of the trachea's, which should permit better mobility during coughing. Expectoration of secretions is, theoretically, improved over that with standard silicone stents. As with the dedicated Dumon stent, the dynamic stent has to be introduced with the help of a special introducer. The risk of migration with this type of stent is much less than with other types. As with any prosthesis, however, the lumen can be plugged by secretions or necrotic debris.

Self-expanding stents were developed initially for vascular and biliary applications; only later were they modified for endobronchial use [36]. For this reason, their physical properties are not ideally suited to the physiological demands of the tracheobronchial tree. Their major advantage is that they can be introduced with the help of the fiber-optic bronchoscope and deployed under fluoroscopic or direct bronchoscopic guidance [37] (fig. 2a, b). Ventilation is more easily maintained during the deployment. On the other hand, these stents also carry a higher risk of irritation of the tracheobronchial tree at their distal and proximal edges. They can also contribute to airway obstruction by recurrent overgrowth of tumour or exuberant granulation tissue through the metallic mesh. Recently, fully covered models have been developed. The long-term success of these stents has yet to be determined.

Recent Developments in Bronchoscopy

Endobronchial Ultrasound

Ultrasound imaging is different from x-ray imaging. The difference in resistance of different tissues to the ultrasound waves (impedance) is more complex and only partly dependent on water content. The different impedance of soft tissues has made ultrasound an indispensable diagnostic tool in medicine. We developed flexible catheters for the Olympus bronchoscopic probes that have a balloon at the tip, which allows circular contact for the ultrasound transducer, providing a complete 360° image of the parabranchial and paratracheal structures. As the saline-filled balloon enhances the ultrasound image, the penetration of the waves produced by the 20-MHz probes is increased. Thus, under favorable conditions, structures at a distance of up to 4 cm can be visualized. The probes have been on the market since 1999 and can be used with regular flexible endoscopes that have a biopsy channel of at least 2.6 mm in diameter [4, 38, 39].

New developments include a special endoscope with an integrated curvilinear electronic transducer at the tip (Olympus BF-UC40P), making possible needle punctures under real-time endoscopic control. The outer diameter of the insertion tube is 5.8 mm. The angulation of the distal end of the endoscope ranges from 160° upward to 90° downward. The endoscope has a small curved, linear-array electronic transducer, 10 mm long, at the distal end of the endoscope in front of a 30° oblique forward-viewing fiber-optic lens (angle of view, 80°). The endoscope has a biopsy channel of 2 mm. The ultrasonic frequency is 7.5 MHz, with a penetration depth of 5 cm. The

scanning direction is parallel to the longitudinal axis of the endoscope, with a scanning angle of 50°, which enables full ultrasonic monitoring of a needle when inserted through the biopsy channel during scanning (fig. 3).

Endobronchial, ultrasound-guided, transbronchial needle aspiration (EBUS-TBNA) has been available for more than 5 years. A growing body of research supports its usefulness in airway assessment and procedure guidance. A growing body of research supports its usefulness in airway assessment and procedure guidance, especially since PET is available [40]. Several authors [41–43] have reported that EBUS-TBNA is a highly accurate and safe method for sampling enlarged mediastinal lymph nodes. These authors also reported that the rate of successful biopsies leading to correct predictions of lymph node staging in lung cancer is higher with EBUS-TBNA than it is with other endoscopy modalities [41–43].

Moreover, EBUS-TBNA was not associated with any complications and, in addition, prevented the need for many invasive procedures. EBUS-TBNA should be considered for staging mediastinal lymph nodes as well as for diagnosing lung cancer. The combined approach of EUS-FNA and EBUS-TBNA [44, 45] may replace more invasive methods in evaluating lung cancer patients in whom hilar or mediastinal metastases are suspected, as well as in evaluating mediastinal or hilar lesions of unknown origin.

Autofluorescence Endoscopy

Early detection and surgical resection of tumours is the only curative treatment for a large majority of lung cancer patients. Early detection with low-dose spiral CT is one of the most promising developments of clinical research [46], but especially in the central airways additional techniques are necessary. Laser-induced fluorescence endoscopy (LIFE) (Xillix Technologies Corp., Richmond, BC, Canada) has facilitated early detection of preinvasive bronchial lesions [3, 47]. However, autofluorescence endoscopy does not distinguish well between preinvasive lesions and other benign epithelial changes, such as bronchitis, which frequently is present in patients whose sputum is suspicious of malignancy or positive for malignancy [48].

Autofluorescence findings have been divided into three classes: normal (class I), inflammation and mild dysplasia (class II), and changes suggesting moderate or severe dysplasia, carcinoma in situ or invasive cancer (class III) [49] (fig. 4). At present, the observed class of autofluorescence does not predict diagnosis; some class III lesions turned out to be class II inflammatory lesions on biopsy [3, 49]. The specificity of autofluorescence en-

doscopy is low, with up to one-third of the areas of abnormal fluorescence representing false positives [49, 50].

Autofluorescence endoscopy may be more useful for detecting preinvasive lesions than white-light bronchoscopy [50]. The results of multicenter clinical trials suggest that autofluorescence endoscopy increases the diagnostic accuracy for squamous dysplasia, carcinoma in situ, and early hilar lung carcinoma when used simultaneously with conventional bronchoscopy [49, 51].

Although several types of autofluorescence systems, such as the LIFE-Lung system described above, the SAFE-1000 (Asahi Optical Corp., Tokyo, Japan), and the D-light system [52] have been developed, all these systems have a low specificity for diagnosing preinvasive lesions. Individuals at high risk for lung cancer also frequently suffer from bronchitis and hyperplasia as a result of cigarette smoking [53, 54]. In a study of the usefulness of autofluorescence endoscopy for detecting preinvasive lesions, we found that out of the 102 sites identified by the D-light system as abnormal, the pathological diagnosis in 51 cases turned out to be hyperplasia, bronchitis, or normal epithelium. This outcome suggests that specific visual diagnosis of preinvasive lesions by autofluorescence endoscopy is still problematic [49].

Autofluorescence endoscopy displays all areas of epithelial thickness and hypervascularity as mild red with suppressed green fluorescence [3, 49, 50, 52]. To improve specificity, color differentiation between preinvasive lesions and bronchitis is necessary.

Electromagnetic Navigation

Unfortunately, flexible bronchoscopy, the least-invasive bronchoscopic procedure, is of limited value for obtaining tissue from lesions in the peripheral segments of the lung. Biopsy success is further compromised if the lesion is <2 cm in diameter [7, 10]. The main limitation of flexible bronchoscopy is the difficulty in reaching peripheral lesions with the accessory tools. Once extended beyond the tip of the bronchoscope, these tools are difficult to guide to the desired location. Localizing the lesion under fluoroscopy is difficult, and alternative diagnostic guidance methods, such as CT-guided bronchoscopy and endobronchial ultrasound, are more demanding. Therefore, new methods for navigation and localization are needed. One of these new technologies is electromagnetic navigation, which is based on virtual bronchoscopy and real-time 3D CT images. The electromagnetic navigation system assists in placing endobronchial accessories (e.g., forceps, brushes, needles) in the desired areas of the lung. The system uses low-frequency

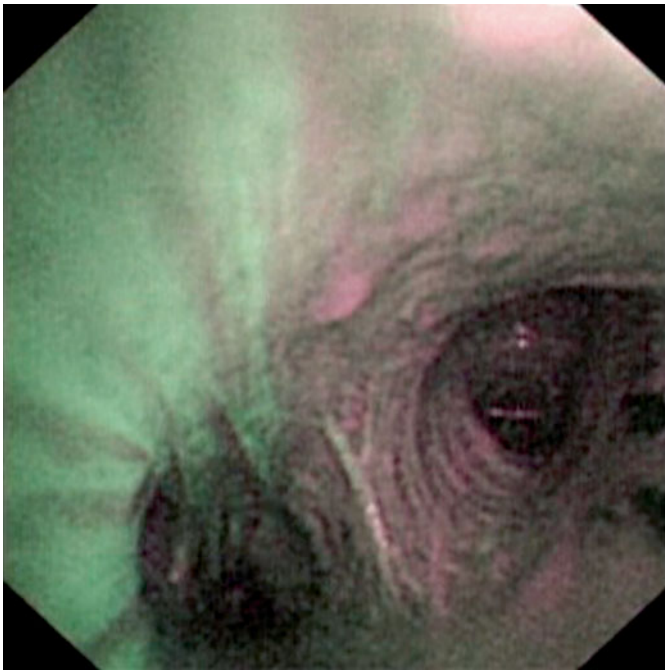


Fig. 4. Pathological autofluorescence in the upper lobe left (histology: squamous cell cancer).

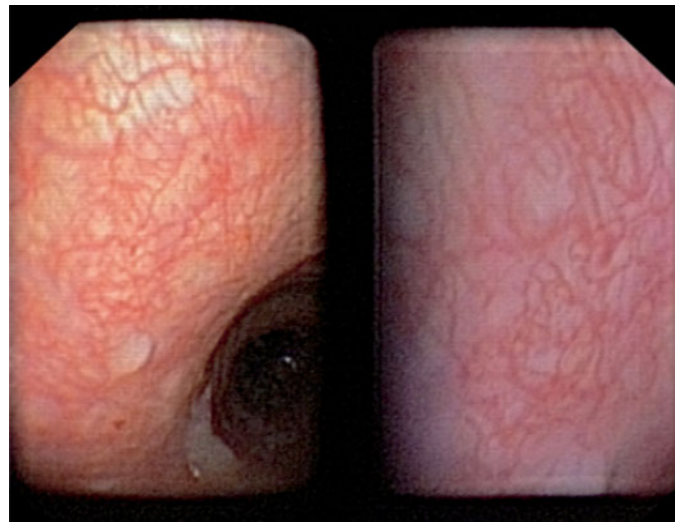


Fig. 6. Magnification of the mucosa (chronic bronchitis).

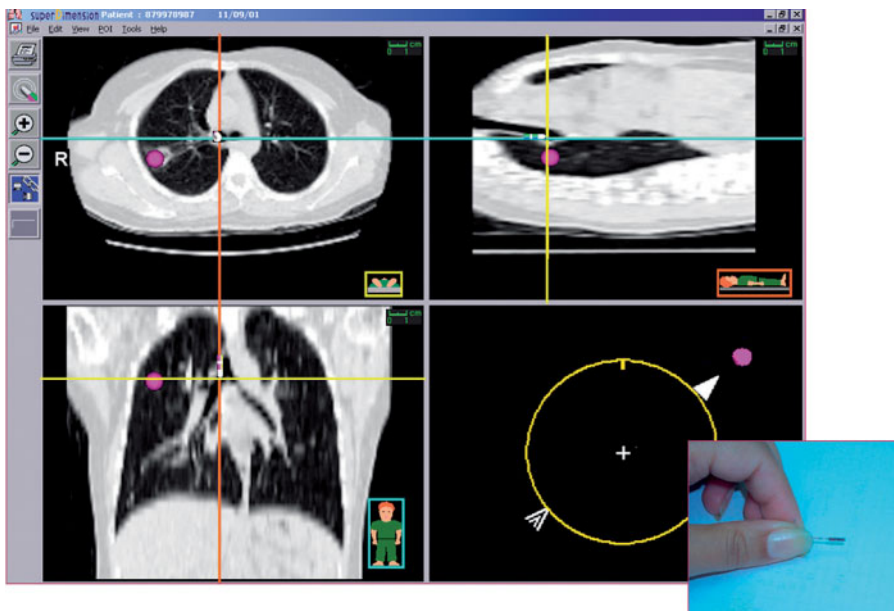


Fig. 5. Electromagnetic navigation. Seen is the probe in the three dimensions on the planning computer tomographies and the way of the probe to the target (right left).

electromagnetic waves, which are emitted from an electromagnetic board placed under the bronchoscopy table mattress. A 1-mm diameter, 8-mm-long sensor probe on the tip of a flexible metal cable (called the locatable guide) constitutes the main assembly of the system. Once the probe is placed within the electromagnetic field, its posi-

tion in the X, Y, and Z planes, as well as its orientation (roll, pitch, and yaw movements) are captured by the system. This information is then displayed on a monitor in real time. The locatable guide also allows its distal section to be steered 360°. The fully retractable probe is incorporated into a flexible catheter (serving as an extended

working channel), which, once placed in the desired location, creates an easy access for bronchoscopic accessories. The computer software and monitor allow the bronchoscopist to view the reconstructed three-dimensional CT scans of the object's anatomy in coronal, sagittal, and axial views, together with superimposed graphic information depicting the position of the sensor probe (fig. 5).

Schwarz et al. [55] performed the first trial to determine the practicality, accuracy, and safety of real-time electromagnetic navigation in locating artificial peripheral lung lesions in a swine model. The study showed a registration accuracy of 4.5 mm on average. No adverse effects, such as pneumothorax or internal bleeding, were encountered in any animal. Schwarz concluded that real-time electromagnetic positioning technology, coupled with previously acquired CT scans, is an accurate technology that can augment standard bronchoscopy to assist in reaching peripheral lung lesions and in performing biopsies.

Becker et al. [56] performed a pilot study in humans based on the results of Schwarz et al. They examined the utility of the system in 30 consecutive patients presenting for endoscopic evaluation of lung nodules and masses. The lesion size in this population varied from 12 to 106 mm but was specifically not controlled for in this early trial. Evaluation was possible in 29 patients, and in 20 patients, a definitive diagnosis was established, with no complications related to the navigation device. Since this study, three other trials have begun to evaluate the value of this technique in sampling small coin lesions.

Promising Techniques

Current research is focused on increasing both diagnostic and therapeutic performance of bronchoscopy. New imaging technologies include: three-dimensional optical and ultrasound imaging; endoscopic zoom technology (allowing endoscopic microscopy); microconfocal scanning microscopy; endoscopic optical coherence tomography, and even endoscopic magnetic resonance tomography. Developments in steering mechanisms, remote control navigation, communication, and nanotechnology should eventually improve sampling success.

Magnification

A high-magnification videobronchoscope combines two systems, a video observation system for high-magnification observation and a fiber observation system for orientating the bronchoscope tip. Whereas conventional white-light videobronchoscopy revealed only increased

redness and local swelling, the high-magnification videobronchoscope enables visualization of the vascular networks, showing increased vessel growth and complex networks of tortuous vessels of various sizes in the bronchial mucosa. Shibuya et al. [57] found that high-magnification videobronchoscopy was useful in detecting dysplastic lesions at sites of abnormal fluorescence. This ability may allow dysplasia to be distinguished from other preinvasive bronchial lesions (fig. 6).

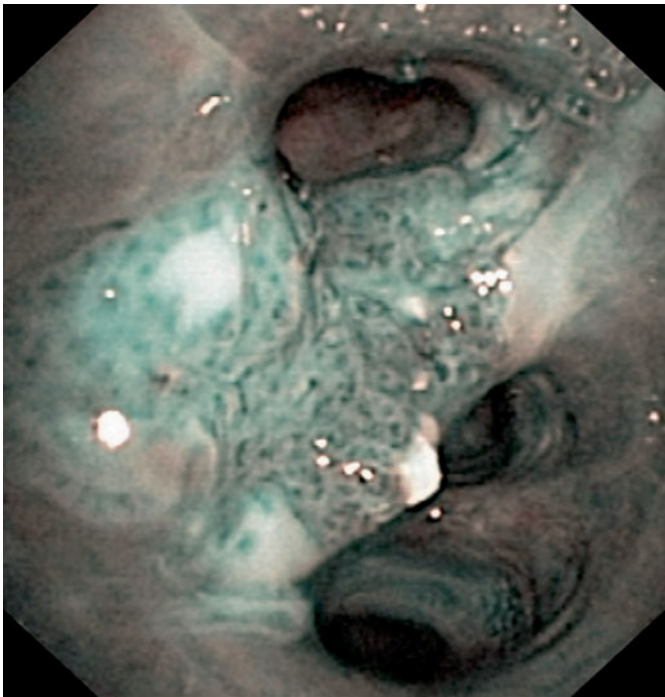
Narrow-Band Imaging

Conventional white-light bronchoscopy uses the full visible wavelength range (400–700 nm) to produce a red-green-blue image. In contrast, narrow-band imaging, in combination with magnification endoscopy, illuminates the tissue surface using special filters that narrow the respective red-green-blue bands while simultaneously increasing the relative intensity of the blue band. This feature enhances the image of the tissue microvasculature, mainly as a result of the differential optical absorption of light by haemoglobin in the mucosa associated with initiation and progression of dysplasia, particularly in the blue range (fig. 7, 8).

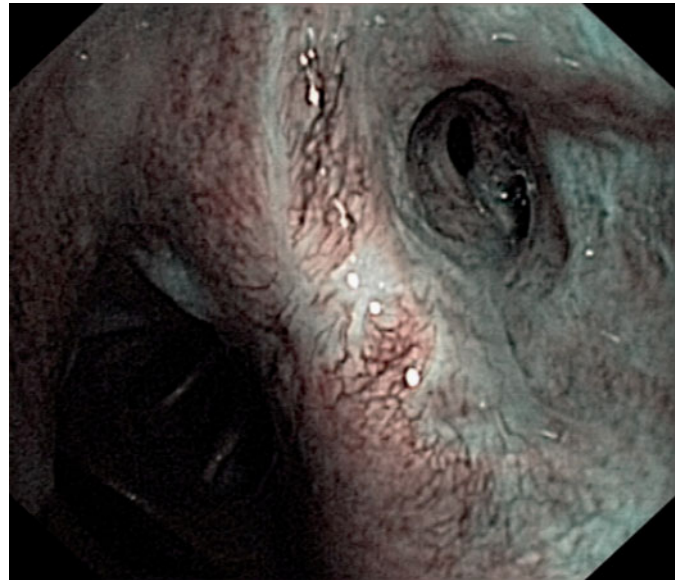
Shibuya et al. [58] published their experience with 48 patients whose sputum was suspicious or positive for malignancy. Observations by conventional high-magnification, white-light videobronchoscopy were made primarily at sites of abnormal fluorescence and were then repeated with narrow-band imaging light to examine the microvascular networks in the bronchial mucosa. High-magnification videobronchoscopy combined with narrow-band imaging was useful in detecting capillary blood vessels in dysplastic lesions at sites of abnormal fluorescence. Similar results were reported by Herth et al. [59]. With the analysis of the microvascular network, better discrimination between benign and premalignant lesions was possible.

Confocal Fluorescence Microendoscopy

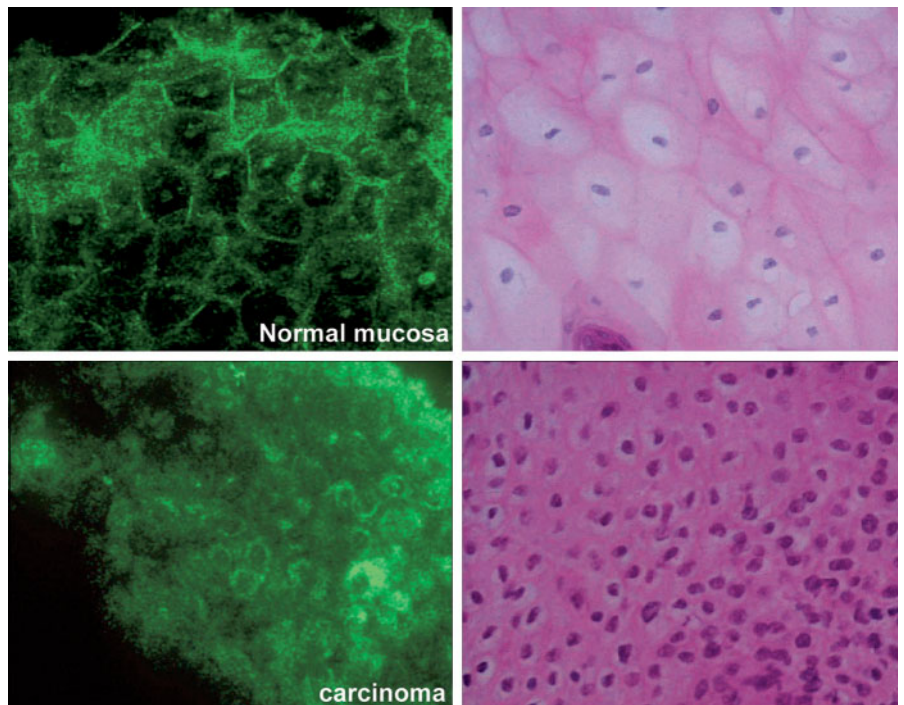
Confocal fluorescence microscopy is indispensable for identifying cellular and subcellular microstructures, offering blur-free, high-resolution images of living and ex vivo biologic samples by reducing out-of-focus light from above and below the focal plane. It obtains optical slices of the sample, consisting of reflected light, autofluorescence, or physiologically and functionally specific exogenous fluorescent agents, such as intravenous fluorescein or topical acetic acid and acriflavine solution. Thus, a stack of depth-resolved optical images can be obtained without physical sectioning. Three-dimensional fluorescence images can then be created to reveal 'histology grade' micro-



7



8



9

Fig. 7. Narrow-band image of a carcinoma in situ. Visible are the dotted, irregular vessels.

Fig. 8. NBI of a severe dysplasia segment 6 right. Visible are the loops and the abrupt-ending vessels.

Fig. 9. Ex vivo images of normal bronchial mucosa and a carcinoma (left: μCOSM images, right: histological control).

morphologic and physiologic details. Confocal fluorescence microscopy can image to depths of approximately 100–300 μm using blue excitation light (440–500 nm). A field of view of approximately 200 × 200 μm² yields cellular details sufficient for diagnostic interpretation.

Despite the fact that we are now on the cusp of ‘virtual histology’ in vivo, several key limitations challenge the clinical utility of confocal fluorescence microendoscopy in isolation, including the necessity for topically applied or intravenously delivered fluorescent contrast dyes,

lack of control over probe placement, and improper probe-tissue orientation, which may interfere with its full potential. Furthermore, surface secretions may result in suboptimal image quality.

Despite the fact that we are now on the cusp of 'virtual histology' in vivo, several key limitations challenge the clinical utility of confocal fluorescence microendoscopy in isolation, including the necessity for topically applied or intravenously delivered fluorescent contrast dyes, lack of control over probe placement, and improper probe-tissue orientation, which may interfere with its full potential. Furthermore, surface secretions (e.g., mucus) may result in suboptimal image quality. Until now the available data are published in the gastrointestinal field. The group of Kiesslich et al. [60–62] could show that cellular, vascular and connective structures can be seen in detail. Graduation of cellular changes with endomicroscopy allows an immediate in-vivo diagnosis of different gastrointestinal diseases. The diagnostic spectrum of confocal endomicroscopy is currently expanding from screening and surveillance for colorectal cancer towards Barrett's oesophagus, *Helicobacter pylori*-associated gastritis and early gastric cancer. The new detailed images seen with confocal laser endomicroscopy are unequivocally the beginning of a new era where this optical development will allow a unique look of cellular structures and functions at and below the surface of the gut.

In the bronchoscopy field, only ex vivo experiences are discussed in expert forums (fig. 9), but the technique will be available in the future.

Conclusions

Today bronchoscopy is a performant tool in the diagnosis of lung cancer and the endoscopic treatment of inoperable lung cancer, and is well established in pulmonology. With the newest available and prototype techniques we can improve the diagnosing and staging in our patients. What is urgently needed, however, is greater acknowledgement of this treatment tool by the specialists in oncology. This will automatically lead to integrational studies on interventional techniques in the algorithmic approach of the inoperable lung cancer patient. Indeed, interventional pulmonologists are too often considered the 'last hope' for widely evolved, (pre)terminal lung cancer patients. An earlier application of interventional techniques in the management of these patients, in collaboration with chemo- and radiotherapists, will most probably have a larger impact on quality of life (and maybe on survival), than each treatment on its own. This is what we, interventional pulmonologists, consider true multimodality treatment of inoperable lung cancer.

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