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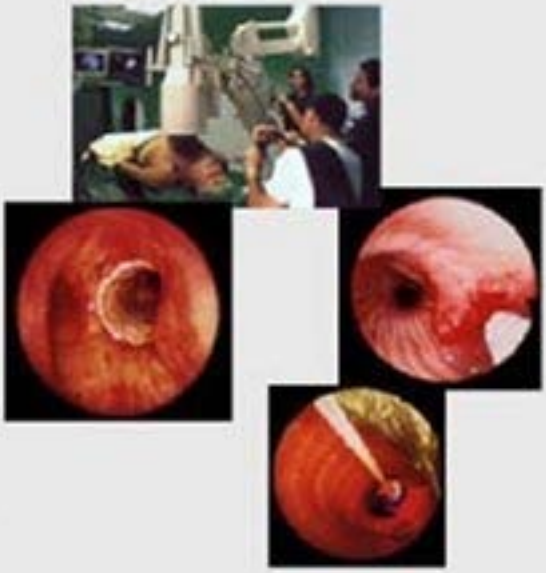
Editor: C.T. Bolliger
Vol. 30

Interventional Bronchoscopy

Editors
C.T. Bolliger
P.N. Mathur



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Progress in Respiratory Research

Vol. 30

Series Editor *C.T. Bolliger,* Cape Town

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Interventional Bronchoscopy

Volume Editors *C.T. Bolliger,* Cape Town
P.N. Mathur, Indianapolis, Ind.

171 figures, 60 in color, and 80 tables, 2000

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Contents

Foreword

When choosing the topic for a particular volume in a scientific book series, the editor is faced with several important questions: should one always choose a 'hot' topic, which is of high interest at the moment, or group-related topics in consecutive books, are the volume editors and the potential chapter authors experts in their fields as well as reliable in submitting their work on time, and of course, is the book sellable, or affordable from the buyer's point of view?

For the first three books as the new series editor of *Progress in Respiratory Research,* I have chosen somewhat related topics. Volume 28 'The Tobacco Epidemic', was a very timely book treating all aspects of smoking, including the wide range of smoking-related disorders. Among these disorders, lung cancer stands out as one of the major threats. As the tobacco companies concentrate their marketing efforts on developing countries, an unprecedented rise in lung cancer can be expected on a global level. New insights into the treatment of this deadly disease have prompted the inclusion of J.H. Schiller's book 'Updates in Advances of Lung Cancer' as volume 29 of the series. New chemotherapeutic agents, and combined-modality treatments involving chemotherapy, surgery and radiation therapy are discussed in that book among other interesting topics.

Despite these advances, the overall prognosis of lung cancer is still dismal, with the 5-year survival rate remaining at about 13%. Apart from metastases, many lung cancer patients die of local intrathoracic complications, obstruction of the central airways being a frequent cause. Therefore, local tumour control often leads to efficient palliation in lung cancer patients with advanced disease. Apart from the tumour-specific treatment options described in Schiller's volume, the rapidly emerging field of interventional bronchoscopy adds a new dimension to the therapeutic armamentarium of lung cancer. Choosing the topic of 'Interventional Bronchoscopy' was therefore a natural extension to volume 29. Treatment of central airway obstruction is, however, just a small part of this new book which covers all aspects of modern diagnostic and therapeutic interventional bronchoscopy, and true to the vision of this book series to promote 'progress' in respiratory research, volume 30 also includes some techniques which are still at an investigational stage. I have undertaken to co-edit the book myself and am very grateful to Prof. Praveen Mathur from Indianapolis for his help in combining all the chapters from authors of both sides of the Atlantic into a state-of-the-art book on bronchoscopy which is of interest to the general reader as well as to the top specialist in the field.

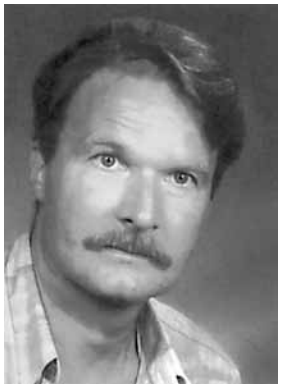
A final comment about the format of this volume. In general, identical format is a top priority of book series. One recognises the series by it, the faithful reader of the series has chosen a certain shelf height where each consecutive volume fits perfectly. So why break all the rules for the current issue? Very simply because of the extensive illustrations, which are necessary for the current topic. We therefore have decided to put function over form for this volume, and make it journal size. We are convinced, the result is a fantastic book.

C.T. Bolliger, Series Editor, Cape Town

Preface

Among the many areas in pulmonary medicine which have been revolutionised by technological advances, bronchoscopy is one of the most obvious examples. Just over 30 years ago, Ikeda introduced the fibre-optic instrument which at the turn of this millennium has practically replaced the rigid instrument for diagnostic procedures in many countries. Parallel to the development of ever finer flexible bronchoscopes and working tools, dramatic advances in imaging techniques of the organs of the chest have become essential for localisation and identification of structures such as lymph nodes, tumours adjacent to bronchial walls, cysts etc., which can be assessed endoscopically to an extent physicians a mere generation ago would not have thought possible. For instance, transbronchial needle aspiration has made sampling of mediastinal lymph nodes a routine endoscopic procedure obviating the need for mediastinoscopies in many patients undergoing pre-operative lung cancer staging.

Apart from this development with the flexible instrument, therapeutic bronchoscopy has come of age, with procedures such as laser resection, electrocautery, argon plasma coagulation, cryotherapy, brachytherapy, photodynamic therapy and stenting, which have all become recognised treatment modalities. For many of the therapeutic procedures, the rigid bronchoscope has witnessed a revival in recent years, as many leading bronchoscopists prefer to use it in circumstances where perfect airway control is mandatory, often when bleeding is a potential threat. Quite often, the rigid and the flexible instruments are used in combination.



C.T. Bolliger

P.N. Mathur

Understandingly, a new term to encompass all these techniques was due to be coined: 'interventional bronchoscopy'. There is emerging consensus that interventional bronchoscopy includes both diagnostic as well as therapeutic procedures which go beyond simple bronchoscopy. The term interventional pulmonology, on the other hand, usually includes interventional bronchoscopy as well as thoracoscopy.

It was the purpose of this book to bring together most of the currently leading interventional bronchoscopists in the world to contribute their knowledge for a state-of-the-art book on interventional bronchoscopy. Contrary to some other books which have appeared recently, this volume, which is volume 30 in the series *Progress in Respiratory Research,* has the role to serve as a textbook on the

one hand, but has to provide the reader with the latest development in the field as well. Thus, the book starts with a historical introduction to bronchoscopy, then deals with the classic chapters on bronchoscopy covering all the topics mentioned above. True to the 'progress' vision of the series some chapters cover emerging areas, such as fluorescence bronchoscopy for the detection of early lung cancer, endobronchial ultrasound, optical diagnostic and therapeutic technologies, virtual bronchoscopy and endobronchial gene therapy. These chapters herald the future of bronchoscopy.

Another two chapters we thought very important for a complete book cover the role of bronchoscopy as an integral part of a patient's management. In the treatment of lung cancer, for instance, endoscopic modalities are often discussed in the bronchology literature, whereas non-endoscopic options appear in the oncological literature, but the relative place and timing of both during the course of the disease is rarely found. The chapters on 'functional evaluation before and after interventional bronchoscopy' and 'multi-modality treatment of advanced pulmonary malignancies' are attempts to make up for this gap in the literature. All in all, the book really covers bronchoscopy from Killian, a good century ago, up to the latest fascinating concept of endoscopic gene therapy for pulmonary neoplasms.

We, the European and the North American editor of this book, were fortunate in basically getting the best people from all over the world to write for us. Many of these authors are regarded as the ultimate authorities in their field of expertise, and the result is this outstanding book. There are some minor overlaps in some topics, i.e. in the two chapters describing the different systems used for fluorescence bronchoscopy which have been accepted deliberately, because some of the statements made are based on preliminary experiences and brand new results. Many of the chapters have been written in the first 6 months of 1999, which will make this book relevant for some years into the new millennium!

'Interventional Bronchoscopy' will appeal to a broad readership, some who look for the latest textbook will have their questions answered, as well as the experienced bronchoscopist, who would like to get the latest information on the cutting edge of research. The publishing house, S. Karger AG, Switzerland, has yet again brought out a book of outstanding quality of print, especially with regard to the many important figures which makes reading this volume an intellectual as well as a visual pleasure.

C.T. Bolliger, Cape Town
P.N. Mathur, Indianapolis, Ind.

General Aspects of Interventional Bronchoscopy

Bolliger CT, Mathur PN (eds): Interventional Bronchoscopy.
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History of the Rigid Bronchoscope

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'Doing easily what others find difficult is talent – doing what is impossible for talent is genius.'

H. Cushing 1928,
H.J. Bigelow lecture in honor to Ch. Jackson [1]

Summary

At the end of the 19th century, three crucial inventions led to the development of the rigid bronchoscope: (1) the detection of local anesthesia, (2) the invention of electricity as a light source and (3) the development of instruments for inspection of the upper digestive and respiratory tract. Gustav Killian of the University of Freiburg combined these techniques and after experimentation dared to apply the new method in man for the first time in 1897. Thereby, he was the first to change the grim fate of those who all too often fell prey to the sequels of foreign body aspiration. He taught generations of physicians the new technique of bronchoscopy, thereby spreading his beneficial invention all over the world. Throughout his life, he continued to improve instruments and applications. In the following years, schools were installed in most continents by pioneers like Chevalier Jackson in the US and Ino Kubo in Japan. They continued Killian's efforts of improving the instruments and technologies for diagnosis and treatment of tracheobronchial and pulmonary diseases. These included the first glass fiber bundles for illumination, special optics for photography and video documentation. It was after Shigeto Ikeda had introduced the flexible fiberscope in 1966 that bronchoscopy spread widely beyond the specialized centers, and the use of the rigid bronchoscope experienced a sharp decline. Only very recently, the advent of interventional techniques such as Nd:YAG laser application and stenting has led to a renaissance of rigid techniques that are widely advised for these and other interventional techniques by the professional societies. Thus, nowadays in worldwide training courses, the use of the rigid bronchoscope is taught again.

In his article entitled: 'Entfernung eines Knochenstücks aus dem rechten Bronchus auf natürlichem Wege und unter Anwendung der directen Laryngoskopie' in volume 38, September 1897, of the *Münchner Medicinische Wochenschrift,* O. Kollofrath, assistant to Gustav Killian at the Poliklinik of Freiburg University, Germany, wrote in the introduction to his report on the first bronchoscopic extraction of a foreign body: 'On March 30th of this year I had the honor to assist my admired principal, Herrn Prof. Killian in extraction of a piece of bone from the right bronchus. This case is of such peculiarity with respect to its diagnostic and therapeutic importance that a more extensive description seems justified' [2]. In order to understand this statement one must consider the state of the art of airway inspection at that time.

The Preendoscopic Era

Access to the airways in the living patient was tried already by Hippocrates (460–370 BC), who advised the introduction of a pipe into the larynx in a suffocating patient. Avicenna of Buchara (about 1000 AD) used a silver pipe for the same purpose. Vesalius' observation around 1542 that the heartbeat and pulsation of the great vessels stopped when he opened the chest of an experimental animal, but returned again after he introduced a reed into the airway and inflated the lungs by the use of bellows mistakenly made him assume that the trachea was part of the circulating system, from which it carried the name 'τραχυσ' ('rough' in Greek language) or arteria aspera ('the rough artery' in Latin) [3, 4].

Desault (1744–1795) advised nasotracheal intubation for treatment of suffocation and removal of foreign bodies. For ages the inhalation of a foreign body in over half of the accidents caused the death or chronic illness of the patient due to purulent infection, abscess, fistulas and malnutrition. Diverse instruments have been designed to remove them blindly from the airways via the larynx or a tracheotomy, called 'bronchotomy', which was also used for treatment of subglottic stenosis such as caused by diphtheria. As until late into the second half of the last century tracheotomy also had a high mortality of up to more than 50% [5], methods were developed for blind intubation. When he presented his 'Treatise on the Diseases of the Air Passages' in 1846, Horace Green however was blamed by the Commission of the New York Academy of Medical Sciences as presenting '... a monstrous assumption, ludicrously absurd, and physically impossible, ... an anatomical impossibility and unwarrantable innovation in practical medicine' and was removed from the society [6, 7]. But Joseph O'Dwyer persisted and introduced the method for emergency intubation of diphtheric children.

The Development of Endoscopy

Although instruments for the inspection of the body cavities such as the mouth, nose, ear, vagina, rectum, urethra and others had been in use for ages, Porter in 1838 still stated: 'There is perhaps no kind of disease covered by greater darkness or posing more difficulties to the practitioner than those of the larynx and the trachea' [quot. in 8]. Because up to then the larynx could be only insufficiently inspected by forcible depression of the tongue with a spatula, a so called 'Glossokatochon', nobody had ever looked into the living trachea. It was only after the advent of three major inventions that direct inspection of the airways and visually controlled treatment became possible: (1) instruments for inspection, (2) suitable light sources and (3) sufficient anesthesia.

The Laryngeal Mirror

Experiments for the inspection of the larynx with the help of mirrors had been performed among others by Latour (1825), Senn (1829), Belloc (1837) Liston (1840) and Avery (1844). However, it was not a physician, but a singing teacher in London, Manuel Garcia, who in 1854, first observed his own larynx by the help of a dental mirror that he had bought from the French instrument maker Charrière in Paris. [9, 10] Without knowing his work almost at the same time, in 1856, the laryngologist Ludwig Türck in Vienna made his first experiments with a similar device, which he lent to the physiologist Czermak of Budapest, when in winter the illumination was no longer sufficient for continuation of his studies. Czermak reported about his findings before Türck, which resulted in a long fight over rights of priority, the so called 'Türkenkrieg' (Turk's war) [11, 12].

By the use of these instruments, diagnosis and treatment of laryngeal diseases became much easier, so that G.D. Gibb in 1862 said [13]:

> 'It has fallen to my lot to see cases of laryngeal disease ... that have existed for ten or twenty years, and submitted to every variety of treatment, without the slightest benefit, at the hands of some of the foremost amongst us, wherein the symptoms have depended upon a little growth attached to one or both vocal chords, which was recognized in as many seconds as the complaints had existed years. The nature of the malady thus being made out, the plan of treatment to be persued became obvious'.

And it was also in 1862 that the German surgeon Victor von Bruns in Tübingen, by the help of this laryngoscopic mirror, could remove the first polyp from a vocal chord in his own brother. Without suitable anesthetics, the procedure needed weeks of preparation by gradual desensitizsation on the patient's side and much training on anatomical preparations and living larynxes of volunteers by the surgeon. Also his report was rejected as '... a daring deed that should not be imitated and the practical importance of which seems less as there would be hardly another opportunity for its repetition.' One of the major problems was the indirect and reverse view of the image, which added to the difficulties [14].

The First Endoscopes and Light Sources

In contrast to other fields of endoscopy, where daylight or candlelight could be introduced for inspection of the vagina, rectum or urethra, it was only after Philipp Bozzini, a general practitioner in Frankfurt had developed his 'illuminator' in 1805 that a suitable light source for the inspection of the trachea came within sight. The still somewhat clumsy device consisted of a box containing a candle, the light of which was reflected by a hollow mirror into a 'conductor', a split metallic tube that could be spread by a simple mechanism. For the inspection of organs that could not be visualized by direct inspection, he used a tube with a mirror for reflection of the light and image. [15].

The first suitable successor was the instrument of Desormeaux, in 1853, who also introduced the word 'endoscope' for his instrument to inspect the body cavities. It was by Desormeaux' endoscope that A. Kussmaul, in 1867/68, performed the first esophagoscopies. [16]. The illumination by spirit, however, was insufficient for the inspection of the stomach. The first suitable gastroscope in 1881 by Mikulicz/Leiter was a closed optic with lenses and prisms that were electrically illuminated at the distal end by a glowing platinum wire which had to be cooled by a constant flow of water and thus was not suitable for application in the airways [17].

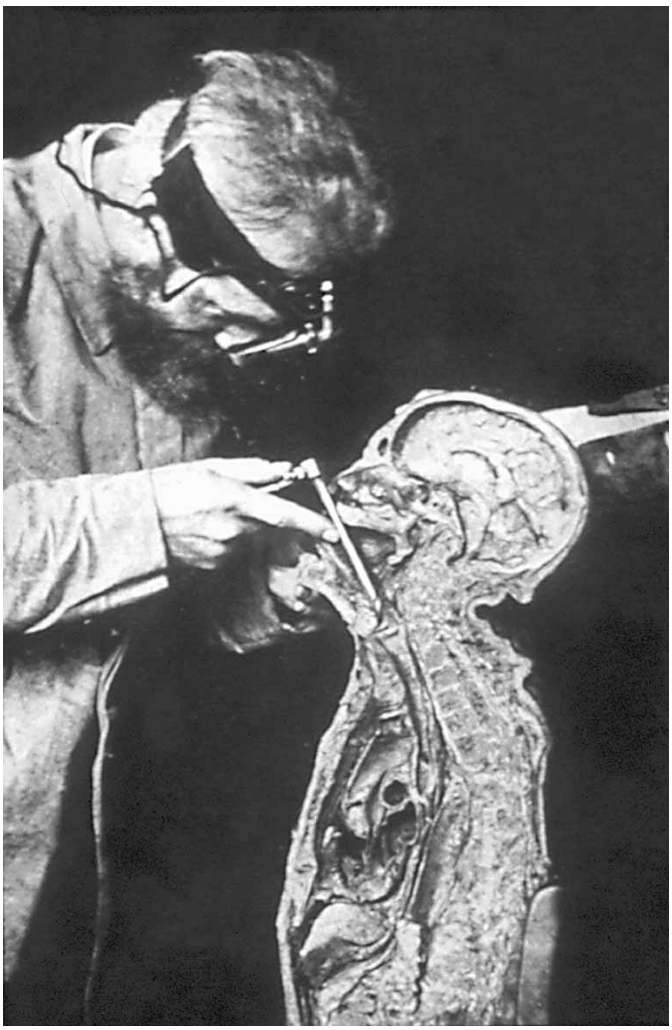
Esophagoscopy was performed mainly by the use of hollow tubes and spatulas that were connected to proximal illumination sources. It was also the Viennese endoscope maker Leiter who in 1886 produced the first so called panelectroscope, a tube that was connected to a handle that contained an electric bulb and a prism for illumination. The instrument was modified by many specialists, such as Gottstein, who was the first to attach a metal tube in 1891, Rosenheim, who accidentally first passed into the trachea, and Kirstein in Berlin. Kirstein intentionally started to intubate the larynx with the esophagoscope and after his first experience in 1894 began systematic direct inspection, which he called 'autoscopy' (Greek 'αυτοσ', himself, meaning directly without help of a mirror). '... I convinced myself ... that one can pass the vocal chords intentionally with a middle sized esophagoscope into the cocainized trachea and right down to the bifurcation; this experience should be eventually fructified.' But as 'The region of the lower trachea is a very dangerous place! ... The rhythmic protrusion of its wall is ... a regular and awe inspring phenomenon, which gives cause for utmost care in introducing rigid instruments', he did not 'fructify', i.e. expand, his experiments [18]. It was the rhinolaryngologist Gustav Killian of Freiburg University who on June 4th, 1895, attended Kirstein's lecture in Heidelberg at the 2nd Congress of the Southern German Laryngologists, who immediately recognized the importance of Kirstein's observation for the diagnosis and treatment of laryngotracheal diseases and began his experiments with the new method.

In 1877, the urologist Nitze of Dresden and the instrument maker Leiter of Vienna had constructed the first lens optic in which electrical illumination was performed by a glowing platinum wire at the distal end which had to be cooled by a constant flow of water when not used inside the urinary bladder such as in von Mikulicz' first gastroscope. Only after in 1879, T.A. Edison had invented the electric bulb which was further miniaturized by Mignon, could distal electric illumination be applied to endoscopy of the airways.

The Development of Local Anesthesia

In his first report on the invention of direct bronchoscopy Killian said: 'Whether one stops inspection with the rigid tube at the bifurcation or passes on for some distance into a major bronchus does not matter for the patient. If he is sufficiently cocainized he does not even realize it' [19]. Before the detection of cocaine many attempts had been made to anesthesize the airways by the use of potassium bromide, ammonia, belladonna, iodine solution, chloroform, morphine and others. Nothing proved sufficient and the patients had to be desensitized by weeks of rehearsing touching of the pharynx and the vocal chords by themselves before a procedure could be performed. The examiner had to be extremely skilled and swift as operations had to be performed within seconds before the view disappeared. Von Bruns advised training on an excised larynx and on a head that had been severed from a corpse and hung from a hook before training on a volunteer '... who certainly could be found rather easily for a little amount of money and would suffer such not really pleasant but not at all painful or dangerous experiments' [14].

Although Morton in Boston had introduced general anesthesia by chloroform already in 1848, its use was so dangerous that it was only rarely applied in laryngoscopic operations. In 1882, a young scientist at the pharmacological institute of Vienna, Sigmund Freud, experimented with cocaine, a sample of which he had bought from Merck Co. [20]. He was eager to make a fortune by a break-through invention in science to be able to marry his fiancé. But to his later dismay, his experiments in withdrawing morphinists from their addiction resulted in disaster. Although he had advised his colleague Koller, an



a

b

Fig. 1. Gustav Killian demonstrating the technique of direct bronchoscopy in a half-dissected frozen corpse sitting on his specially designed examination chair which keeps the patient's back in a straight position to enhance introduction of the endoscope. A laryngoscopic spatula is in situ, and light is introduced from an electric head lamp (**a**). In the supine position he demonstrates how local anesthesia is applied to the trachea by a cotton swab before the bronchoscope is introduced (**b**).

eye specialist, to use cocaine solution for pain relief when he suffered from severe conjunctivitis, he failed to recognize the importance of his observation himself that cocaine caused numbness when he put it to his tongue. Koller, however immediately realized the importance of this observation and after feverishly experimenting with this new 'miracle drug' on rabbits and patients inaugurated local anesthesia in his lecture on September 15th, 1884, at the Annual Congress of German Ophthalmologists in Heidelberg. At the same time the Viennese laryngologist Jellinek introduced cocaine as local anesthetic for the inspection of the airways [quot. in 8]:

'By eliminating the reflexes of the pharynx and the larynx it was possible to perform some of the operations in which even the most skillful artists in surgery had failed. The procedure completely changed. Virtuosity gave way to careful methodology, skill to exactness and the former almost endless preparation that so often tried the patience of the physician as well as of the patient could be almost completely abandoned'.

Thus the way was paved for Gustav Killian to pursue his experiments with bronchoscopy after he had attended Kirstein's lecture in Heidelberg.

Gustav Killian and the Invention of Bronchoscopy

Gustav Killian was born on the 2nd of June, 1860, in Mainz on the Rhine. After graduation from high school in 1878 he began to study medicine at the university of Strassburg, where one of his teachers was Adolf Kussmaul. After 1880, he continued clinical education at Frei-

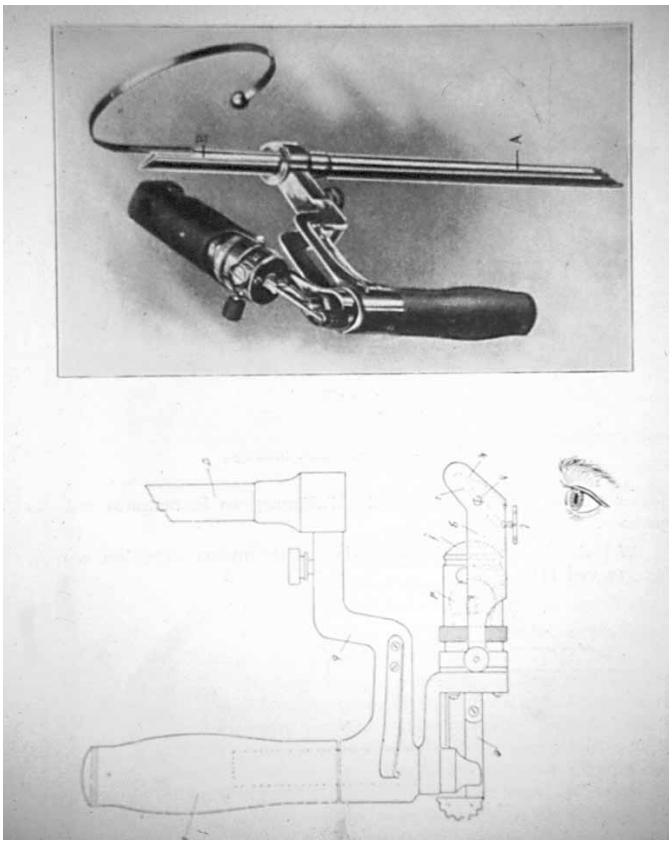


Fig. 2. Brünings' modification of the bronchoscope. The electroscopic handle is connected to the intubation endoscope through which the bronchoscope proper is then introduced. To prevent inadvertent damage by uncontrolled sliding of the bronchoscope, a spring is attached which keeps it fixed in the chosen position and also serves as measure for depth of introduction.

burg, Berlin and Heidelberg, where he passed his final examination in 1882. Afterwards, he started practical work at the municipal hospital of Mannheim close to Heidelberg and later in Berlin to get an education in ENT medicine by Hartmann and Fraenkel. As he could not find employment Killian settled down as practitioner in Mannheim in 1887. Four months later he already left again when he was offered to become head of the section of rhinolaryngology at Freiburg that was part of the large faculty of internal medicine. [3, 21].

At the meeting of the South German Laryngological Society in Heidelberg in 1889, he gave a short report on a new technique for examination of the dorsal wall of the larynx. Killian learned about Kirstein's new technique at the meeting of the Laryngological Society in Heidelberg in 1895. Because of the experiences of Pieniazek [22] at Krakau, who had introduced direct lower tracheoscopy via tracheostomy without any complications, Killian at once realized the potentials of this new method of direct inspection of the trachea and in 1896 began experimental work. In tracheotomized patients he passed the bifurcation with the 'bronchoscope', a somewhat modified esophagoscope of Rosenheim and noticed that the bronchi where elastic and flexible and he was 'stopped only when the diameter of the tube was surpassing that of the bronchi'.

After he had confirmed his findings in corpses without tracheotomies as well (fig. 1) he dared to perform the first direct endoscopy via the larynx in a volunteer. He noticed the flexibility of the trachea and how easily he could adjust it to the angle of the main bronchi and introduce the endoscope down to the lobar level. 'I think I have made an important discovery' he noted afterwards. Bronchoscopy was born. In the same year, 1897, he removed the first foreign body via the translaryngeal route on which his pupil Kollofrath [2] reported in his paper.

After further experience and removal of two more foreign bodies, Killian felt safe to present his new method of 'direct bronchoscopy' at the 6th meeting of the Society of South German Laryngologists at Heidelberg on May 29th 1898, and in the same year, his first publication on direct bronchoscopy was printed (*Münchner Medicinische Wochenschrift* vol 27, Juli 5th, 1898] [19]. The following years at Freiburg were full of technical improvements of the new method and with the quest for more and more indications of its use (fig. 2) He published 34 papers concerning discovery, technique and clinical application of his invention. In 1900, he received the award of the *Wiener Klinische Wochenschrift* for his paper on 'Bronchoscopy and its Application in Foreign Bodies of the Lung'. Due to his publications and many lectures, he was very famous, and Freiburg became the Mekka of bronchoscopy. Hundreds of physicians came from all over the world (the list of participants notes 437 foreign guests from all continents, more than 120 from the US), and up to 20 training courses had to be held every year (fig. 3). He was invited as a very popular speaker all over Europe, and patients were sent to him from as far as South America for treatment of foreign bodies [23].

In order to fully understand the importance of endoscopic removal of foreign bodies, one has to consider the state of thoracic surgery at Killian's time. Most of the patients fell chronically ill after the aspiration of a foreign body, suffering from atelectasis, chronic pneumonia and hemorrhage to which half of them succumbed if untreated. Surgical procedures were restricted to pneumoto-

my when the bronchus was occluded by extensive solid scar tissue, the foreign body could not be reached by the bronchoscope, and it had a very high mortality rate. Lobectomy or pneumonectomy could not be performed before Brunn and Lilienthal developed the surgical techniques for lobectomy after 1910 and Nissen, Cameron Haight and Graham introduced pneumonectomy after 1930 because techniques for safe closure of the bronchial stump were missing [24].

Thus for those who where confronted with these patients, it must have seemed like a miracle that already shortly after the introduction of bronchoscopy, almost all patients could be cured. According to a statistical analysis by Killian's pupil Albrecht of 703 patients with aspiration of foreign bodies during the years 1911–1921, in all but 12 cases the foreign body could be removed bronchoscopically, although many had remained inside the airways for a considerable time, a success rate of 98.3% [25]. In the light of this situation, Killian's triumphant remarks become understandable when he states [22]:

'One has to be witness when a patient who feels himself doomed to death can be saved by the simple procedure of introducing a tube with the help of a little cocaine. One must have had the experience of seeing a child that at 4 pm aspirated a little stone, and that, after the stone has been bronchoscopically removed at 6 pm, may happily return home at 8 pm after anesthesia has faded away. Even if bronchoscopy was ten times more difficult as it really is, we would have to perform it just for having these results'.

Besides numerous instruments for foreign body extraction, other devices as for example a dilator and even the first endobronchial stent where constructed [26] (fig. 4). Although the development of bronchoscopy was Killian's main interest in the years at Freiburg he pushed ahead in other fields too. He developed the method of submucosal resection of the septum and a new technique for radical surgery of chronic empyemata of the nasal sinuses with resection of the orbital roof and cover by an osseous flap [27]. In about 1906, he began intensive studies of the anatomy and the function of the esophageal orifice and found the lower part of the M. cricopharyngeus to be the anatomical substrate of the upper esophageal sphincter. According to his observations it was between this lower horizontal part and the oblique upper part of the muscle that Zenkers pulsion diverticulum developed, where the muscular layer was thinnest. One of his scholars, Seiffert, later developed a method of endoscopic dissection of the membrane formed by the posterior wall of the diverticulum and the anterior wall of the esophagus.

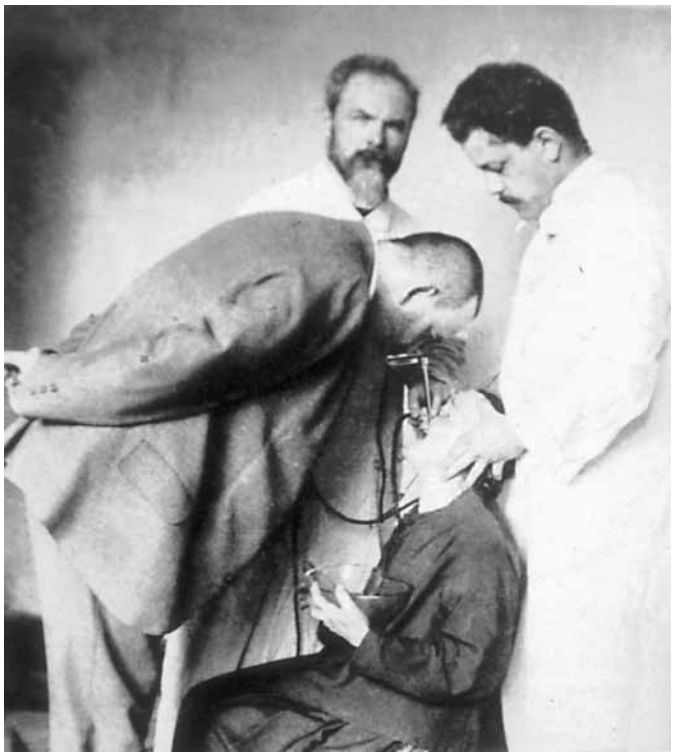
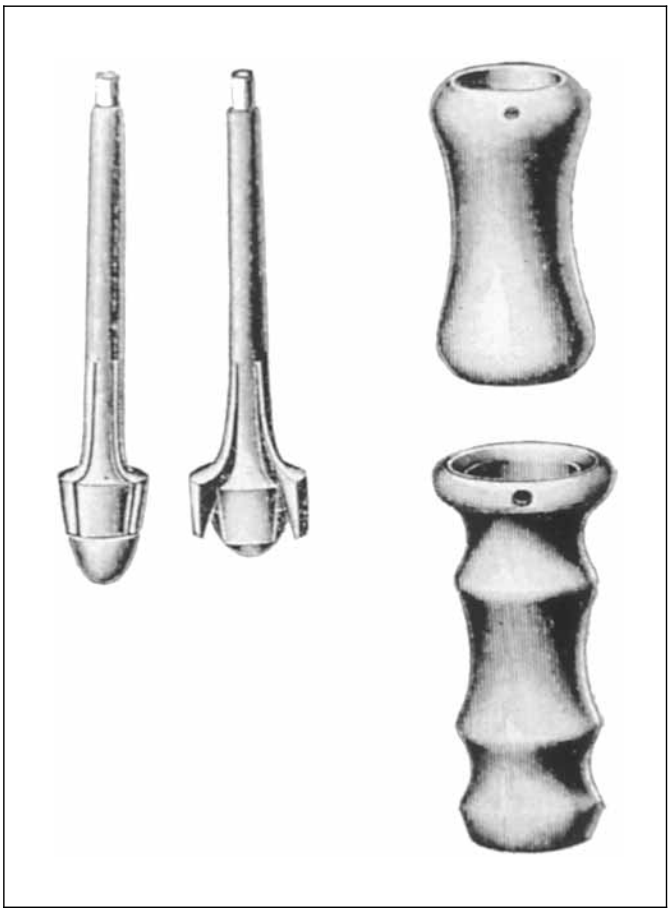


Fig. 3. G. Killian and his assistant and later successor as head of the department in Berlin, C. von Eicken, demonstrate bronchoscopy to a colleague.

In 1907 he received an invitation by the American Otorhinolaryngological Society, and it was on his triumphant journey through the US that on July 3rd 1907, he gave a lecture on these findings at the meeting of the German Medical Society of New York, which was also published in *Laryngoscope* in the same year [28]. Lectures were followed by practical demonstrations of his bronchoscopic and surgical techniques and by banquets at night. On his journey he visited Washington, where he had a brief encounter with Theodore Roosevelt. At Pittsburgh he met Chevalier Jackson, then already outstanding pioneer of esophagobronchology at the University of Pennsylvania. He was awarded the first honorary membership of the Society of American Otorhinolaryngology and also became an honorary member of the American Medical Association and received a medal in commemoration of his visit [22].

As Killian was the most famous laryngologist of Germany, when Fraenkel at Berlin retired in 1911, he became successor to the most important chair of rhinolaryngology. Although bronchoscopy seemed to have reached its peak, he felt that visualization of the larynx was unsatis-



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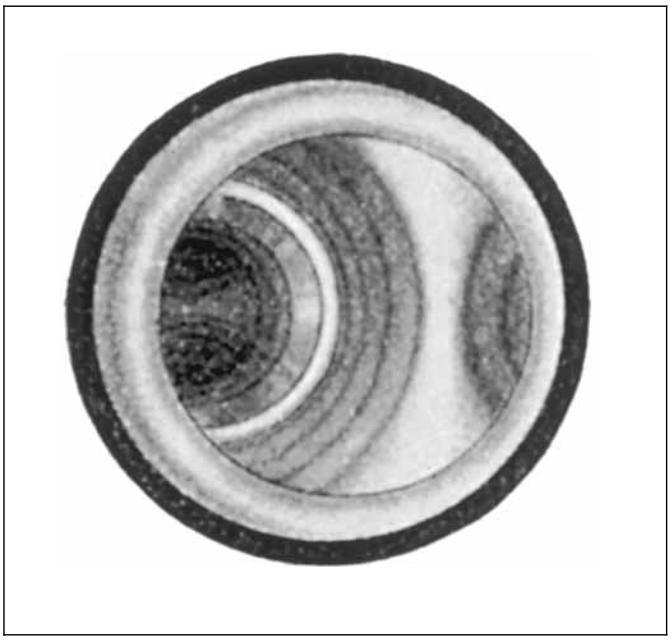

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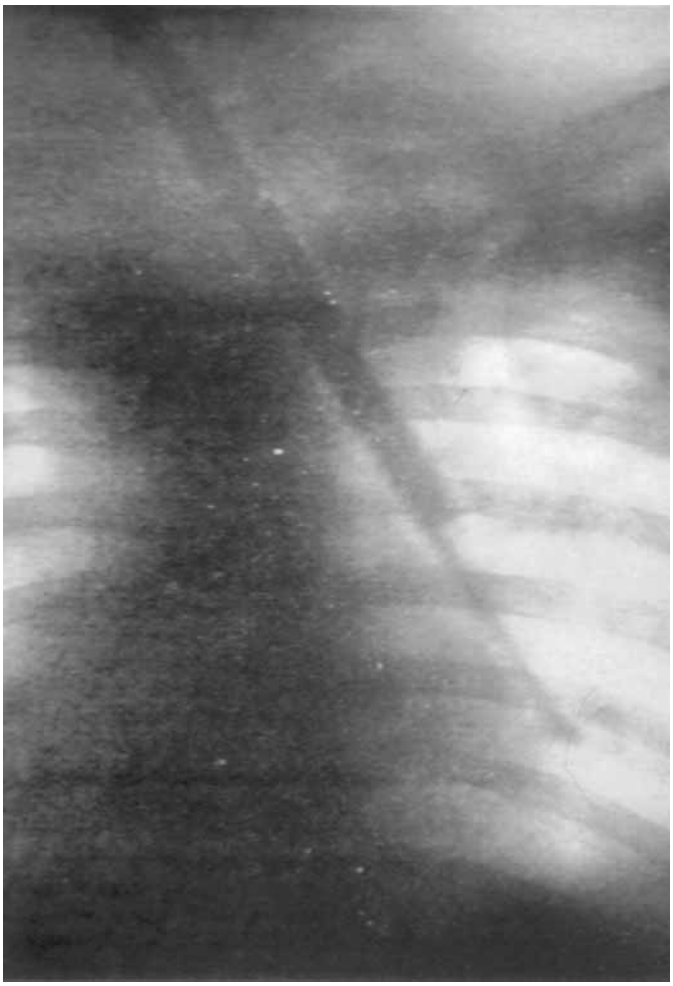
Fig. 4. Implantator and hard rubber stents for treatment of bronchial stenosis after removal of foreign bodies (**a**) and a stent in situ in the left main bronchus (**b**).

factory. Using Kirstein's spatula, Killian realized that inspection of the larynx in a hanging position of the head was much easier and had a special laryngoscope constructed that could be fixed to a supporting construction by a hook, a technique he called 'suspension laryngoscopy' by which he could use both hands for manipulation [29]. His assistant Seiffert improved the method by using a chest rest, a technique that later was brought to its perfection by Kleinsasser and is still used for endolaryngeal microsurgery.

In 1911, Killian had been nominated Professor at the Kaiser Wilhelm Military Academy of Medicine, and as during World War I he had to treat laryngeal injuries, he visited the front line in France where he also met his two sons who were doing service there. After his return, he founded a center for the treatment of injuries of the larynx and the trachea. During this era, he was very much concerned with plastic reconstruction of these organs, especially as he could refer to the work of Dieffenbach and Lexer, two of the most outstanding plastic surgeons of their times, who had also worked in Berlin. His article on the injuries of the larynx was to be his last scientific work before he died from gastric cancer in 1921.

During his last years, Killian prepared several publications on the history of laryngotracheobronchoscopy [30]. For teaching purposes, already in 1893, he began illustrating his lectures by direct epidiascopic projection of the endoscopic image above the patient's head. Phantoms of the nose, the larynx and the tracheobronchial tree were constructed according to his suggestions [31]. Due to his always cheerful mood, he was called the 'semper ridens' (always smiling) and in his later years, his head being framed by a tuft of white hair, his nickname was 'Santa Claus'. He created a school of laryngologists and his pupils dominated the field of German laryngology and bronchology for years. Albrecht and Brünings [25] published their textbook of direct endoscopy of the airways and esophagus in 1915. Like von Eicken in Erlangen and Berlin and Seiffert in Heidelberg, they had become heads of the most important chairs of otorhinolaryngology in Germany. It



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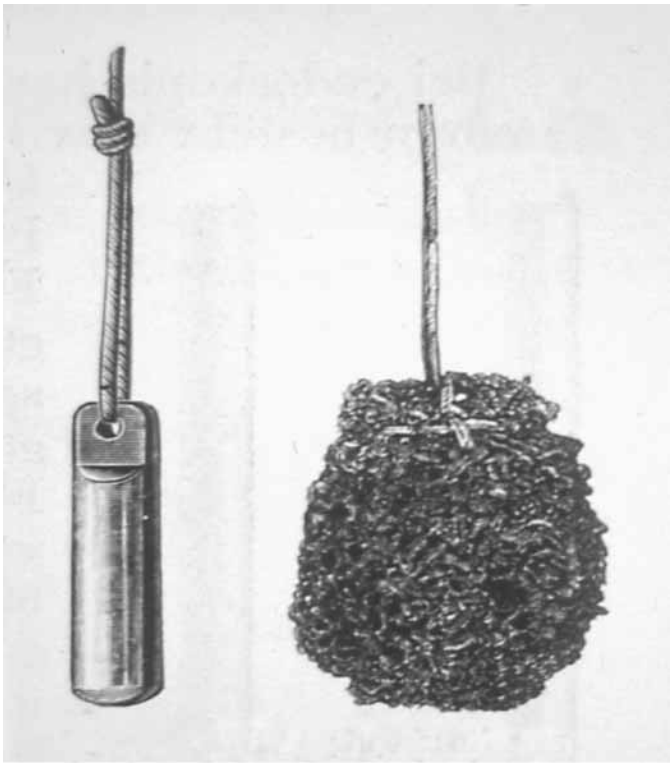

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Fig. 5. Rigid bronchoscopy under X-ray examination for probing peripheral bronchi.
Fig. 6. Metallic capsule containing mesothorium as radioactive source which is kept in place inside the airway by wrapping a rubber sponge around it.

was through him that the separate disciplines of rhinolaryngology and otology were combined. When Killian died on February 24th, 1921, his ideas had spread around the world. Everywhere skilled endoscopists developed new techniques, and bronchoscopy became a standard procedure in diagnosis of the airways. His work was the basis for the new discipline of anesthesiology as well, providing the idea and instruments (laryngoscope by Macintosh) for the access to the airways and endotracheal anesthesia.

Through all his professional life Gustav Killian kept on improving and inventing new instruments and looking for new applications. He applied fluoroscopy, which had been detected by K. Roentgen of Würzburg in 1895, for probing peripheral lesions and foreign bodies [32] (fig. 5). To establish the X-ray anatomy of the segmental bronchi, he introduced bismuth powder [33]. He drained pulmonary abscesses and instilled drugs for clearance via the bronchial route, and he even used the bronchoscope for 'pleuroscopy' (thoracoscopy) and transthoracic 'pneumoscopy' when abscesses had drained externally [34]. Foreign bodies that had been in place for a long time and had been imbedded by extensive granulations were successfully extracted after treatment of the stenosis by a metallic dilator and in case of restenosis, metallic or rubber tubes were introduced as stents. Although cancer then was a comparatively rare disease (31 primary and 135 secondary cancers in 11,000 postmortems), he pointed out the importance of pre- and postoperative bronchoscopy [35]. Already in 1914, he described endoluminal radiotherapy in cancer of the larynx by mesothorium [36] and in the textbook of his coworkers Albrecht und Brünings [25] published in 1915, we find the first description of successful curing of a tracheal carcinoma after endoluminal brachyradiotherapy (fig. 6). In taking special interest

in teaching his students and assistants to maintain high standards in quality management by constantly analyzing the results of their work and always keeping in mind that he was standing on the shoulders of excellent pioneers, he kept up the tradition among the most excellent in his profession, like Billroth of Vienna. In his inaugural lecture in Berlin on November 2nd, 1911, he pointed out that it was internal medicine from which the art spread to the other faculties, and that patience and empathy should be the main features of a physician, but on the other hand persistence in following one's dreams was important because 'to live means to be a fighter'. He ignited the flame of enthusiasm in hundreds of his contemporaries who spread the technique to other specialties, thus founding the roots for contemporary interventional procedures like microsurgery of the larynx (Kleinsasser) and intubation anesthesia (Macintosh, Melzer and Kuhn).

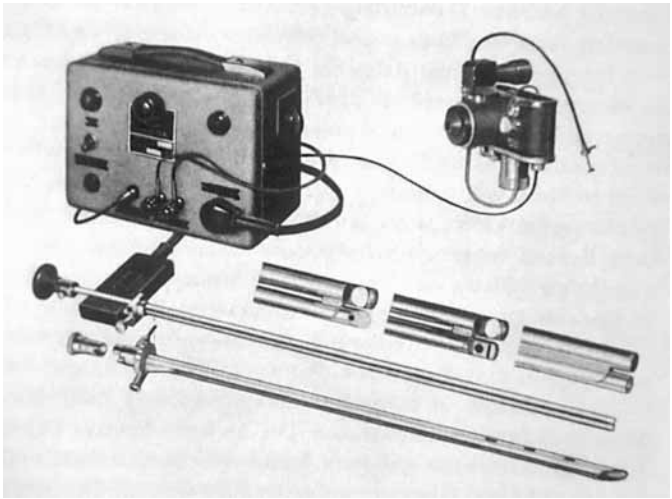

Fig. 7. Rigid bronchoscopes with distal flash and photographic apparatus used by A. Huzly.

Rigid Bronchoscopy in the 20th Century

Main Schools

Due to the enthusiastic activities of Killian and his assistants in teaching and spreading the new technique, hundreds of specialists all over the world had learned bronchoscopy, and many improvements were added to the instrument. Thus, already by 1910, Killian had collected 1,116 papers on esophagoscopy (410), gastroscopy (34) and laryngotracheobronchoscopy (672) for his paper on the history of bronchoscopy and esophagoscopy [30]. It was hardly possible to follow all traits in every continent, where soon after the introduction by pioneers separate schools developed.

Killian's coworkers von Eicken, Albrecht, Brünings, Seiffert and others for decades held the chairs of all important departments in Germany for decades. They improved Killian's instruments and introduced new methods, such as endoscopic treatment of Zenker's diverticulum by Seiffert, who also developed the chest rest for laryngoscopy (1922) which was perfected by Kleinsasser to the current device for microlaryngoscopy (1964). Unfortunately, after World War II the development took separate ways until recently. In Western Germany, Huzly in Stuttgart was the most prominent proponent of rigid bronchoscopy, who in 1961 edited his photographic atlas of bronchoscopy [37] (fig. 7). Riecker introduced relaxation by curare in 1952, which was replaced by succinylcholine by Mündnich and Hoflehner in 1953. Maassen introduced bronchography via double lumen catheter in 1956. Two companies, Storz and Wolf became the most important instrument makers in Germany and introduced new technologies such as the Hopkins telescope and television cameras (fig. 8). In our days among others Dierkesmann, Freitag, Häussinger, Macha and Becker are the proponents of rigid bronchoscopy for the development and performance of interventional procedures such as laser treatment, stenting and photodynamic laser therapy. In Eastern Germany, Friedel developed the first ventilation bronchoscope (1956) which was modified by Brandt (1963) (fig. 9), who edited an extensive textbook on endoscopy of the air and food passages in 1985, in which he reported on more than 100 successful treatments by endobronchial stenting which he already began in the early 70ies [38]. In the same year as E. Schiepatti of Buenos Aires wrote about transtracheal puncture of the carinal lymph nodes, Euler reported on pulmonary and aortic angiography by transbronchial puncture in 1948/49 and later on the technique of rigid transbronchial needle aspiration for mediastinal masses in 1955 which was further perfected by Schiessle in 1962 [39].

In the US where A. Coolidge on May 11th, 1898, performed the first lower tracheobronchoscopy at the Mass. General Hospital [6], it was Chevalier Jackson in Philadelphia, whom Killian had met on his visit to the US in 1907, who, together with his instrument maker Pillings, made many improvements in instruments for bronchoscopy and esophagoscopy and became the 'father of American bronchoesophagology'. During his training to become

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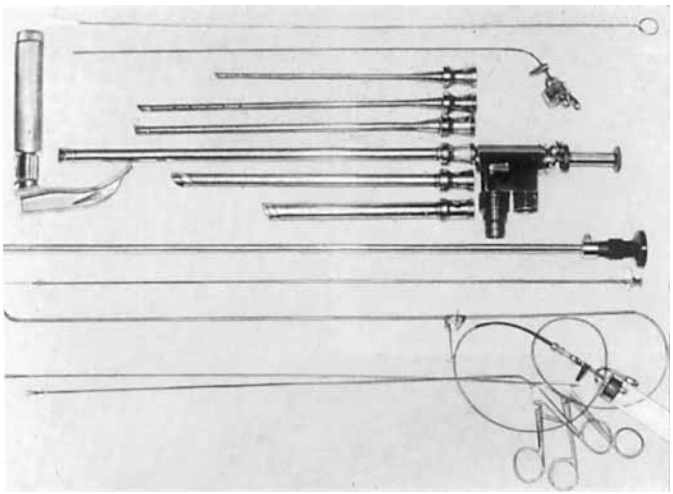

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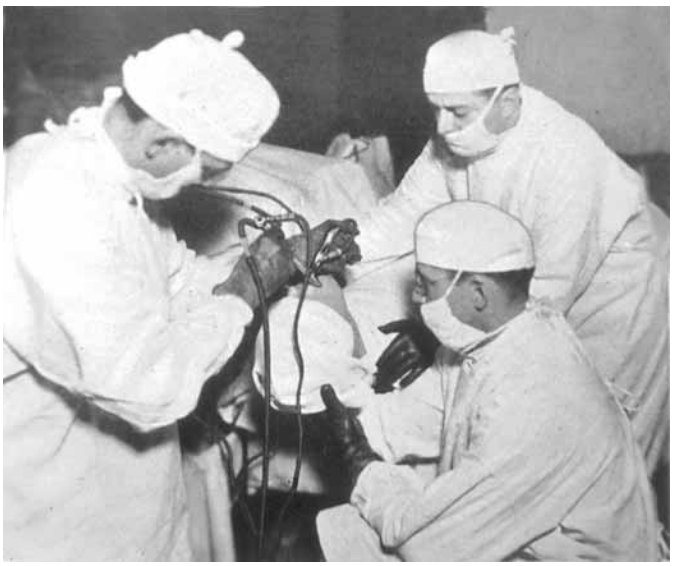
Fig. 8. Bronchoscopy with television camera by Wolf Co. in 1958.
Fig. 9. Bronchoscope set by Friedel with special ventilation port which is combined with the connector for illumination.
Fig. 10. Minimum endoscopic instrument set in a transportable case made by Pillings as suggested by Ch. Jackson.

a laryngologist, he had visited London in 1886, where he was shown the 'impractical device designed by Morel Mackenzie in an effort visually to inspect the esophagus' [40]. In 1890, he constructed the first endoscope 'worthy of the name' for esophagoscopy, and in 1904, he constructed the first American bronchoscope. After Einhorn in New York had added an integrated light conductor and Fletcher Ingals of Chicago had introduced distal illumination to the esophagoscope, Jackson equipped his bronchoscope with a light carrier with a miniaturized electric Mignon bulb at the distal end and with an additional suction channel (fig. 10). Confronted by many patients suffering from aspiration of foreign bodies he invented many instruments for retrieval. In 1907, he published the first systematic textbook on bronchoesophagology which he dedicated to Gustav Killian, the 'father of bronchoscopy'. In this book, he already addressed modern issues of quality management such as analysis and prevention of complications and rational construction of bronchoscopy suites and arrangement of equipment and staff (fig. 11). Being a thorough philanthropist he constantly refused to have his inventions patented, as he wanted them to be spread as widely as possible, and by his persistence with the government he pushed a law for the prevention of accidents by ingestion of caustic agents. He was a perfectionist in techniques and totally convinced that teaching had to be performed on animals before treating patients. Therefore, he always refused to go back to England, where



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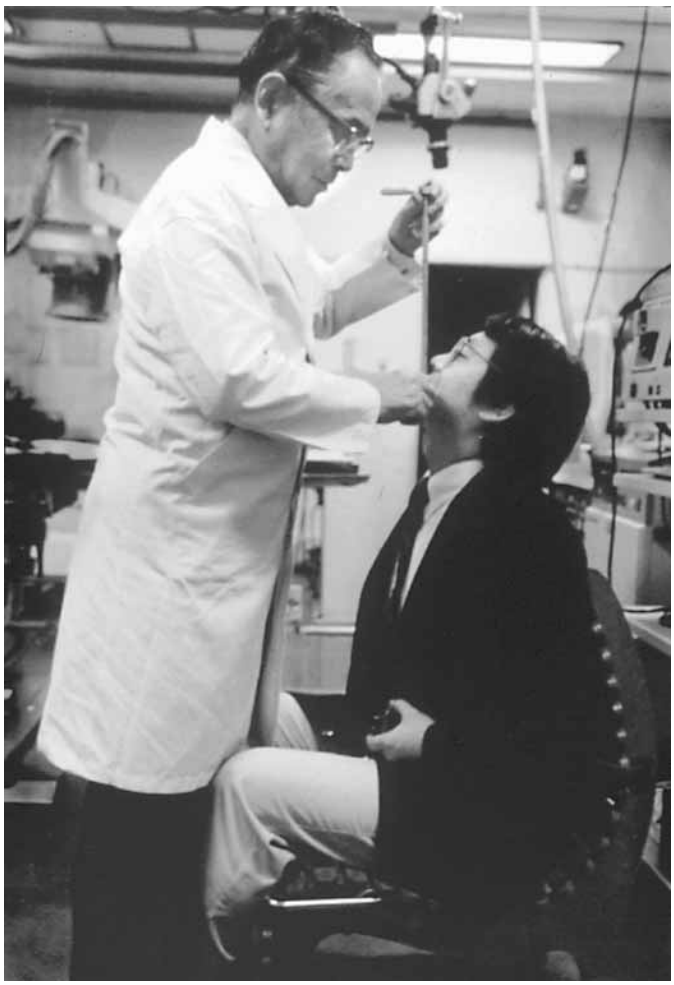

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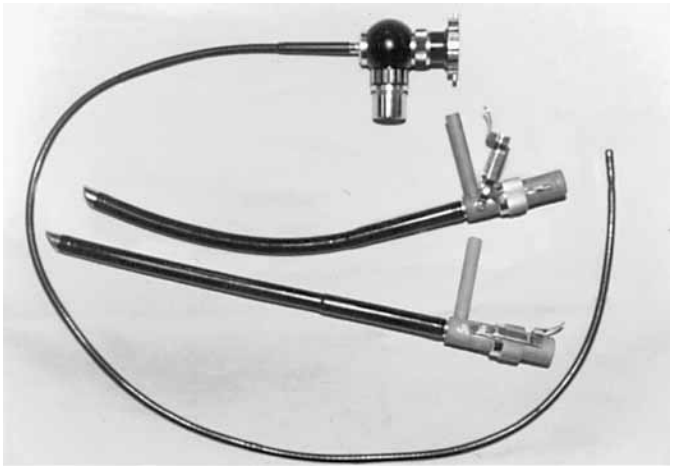
Fig. 11. Rigid bronchoscopy as performed by Jackson. Note the assistant holding the patient's head throughout the procedure.
Fig. 12. Shigeto Ikeda demonstrates introduction of the rigid bronchoscope in the sitting position on one of his assistants who is strapped on Killian's examination chair.

animal rights activists prevented such training courses. In 1928, in recognition of his 'conspicuous achievements in the broad field of surgical science' he was awarded the Bigelow Medal by the Boston Surgical Society which was presented to him by H. Cushing 'for his eminent performances and creative power by which he opened new fields of endeavor' and in acknowledgement of his 'indefinable greatness of personality' [1]. He simultaneously held five chairs of laryngology at different hospitals in his hometown Pittsburgh and in Philadelphia. His son Ch. L. Jackson also became a laryngologist and was his successor at the Temple University of Philadelphia. He was the founder of the Pan American Association of Otorhinolaryngology and Bronchology and of the International Bronchoesophagological Society and cofounder of the World Medical Association. Together with his father, he edited the last issue of the textbook [41].

Their school extends well into our time, as many of today's specialists' teachers were trained by the Jacksons, such as E. Broyles in Baltimore, who after additional training by Haslinger in Vienna introduced the telescope optic for bronchoscopy in 1940, the optical forceps in 1948 and fiber illumination for the rigid bronchoscope in 1962. His scholar G. Tucker became professor at Jefferson in Philadelphia, where he trained B. Marsh who keeps the tradition into our days together with Ch. M. Norris. P. Hollinger and Brubaker, who became specialists in pediatric bronchoscopy, introduced color photography in the 40ies. Hollinger's son today is a famous pediatric laryngologist. Andersen was the first to perform bronchoscopic transbronchial lung biopsy via the rigid bronchoscope in 1965. Sanders, in 1967, introduced jet ventilation for rigid bronchoscopy.



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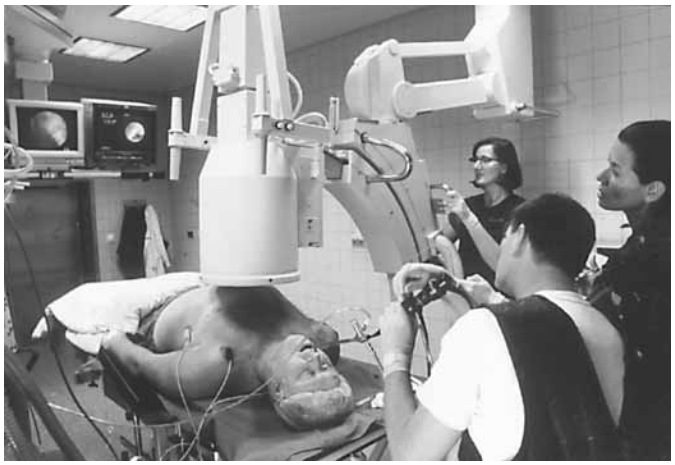

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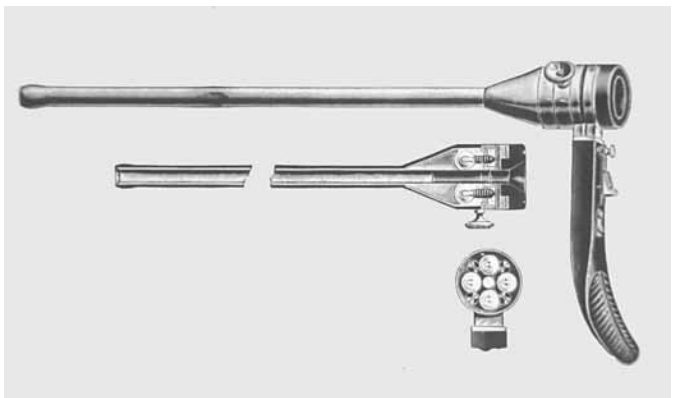

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Fig. 13. Prototype of a flexible bronchoscope and the orotracheal tube that is straightened by a locking mechanism for introduction of rigid instruments.
Fig. 14. Bronchoscopy combining the rigid bronchoscope with jet ventilation and flexible instruments for interventional procedures using video documentation and fluoroscopy.
Fig. 15. First cold light illumination system by v. Schrötter of Vienna. The light from four electric bulbs at the proximal end is transported via a ring shaped plexiglass light guide to the distal end of the endoscope.

After staying with Killian in Freiburg, it was Inokichi Kubo of Kyushu University in Fukuoka who first introduced bronchoscopy to Japan in 1907. He was joined by S. Chiba, who, after training with Brünings, stayed in Tokyo from 1910. Joe Ono, who was trained by Jackson in 1934, founded the Japan Bronchoesophagological Society in 1949. Shigeto Ikeda, who later developed the flexible fiberscope, introduced glasfiber illumination for the rigid bronchoscope in 1962. When Ikeda, who found rigid bronchoscopy under local anesthesia in the sitting position on 'Killian's chair' cumbersome (fig. 12), introduced the flexible bronchoscope, he used it in combination with a flexible tube that could be straightened by a locking mechanism so that he was still able to introduce the rigid optic in the same session (fig. 13). In the era of expanding interventional procedures, this method of combining both the rigid and the flexible endoscope today regains new attention (fig. 14) [42].

Technical Developments

Illumination. After the advent of the electrical bulb, illumination became sufficient for the illumination of the airways. At first, the lamps were installed separately on statives or fixed to a head rest, from where the light was reflected into the endoscope. Connection of the light source to the endoscope improved handling considerably. Thus, Killian and his coworkers preferred to use Casper's panelectroscope, in which the light bulb was integrated into the handle, from where it was reflected by a prism to the endoscope because it was not so easily soiled by secretions. Jackson, however, used distal illumination via a light guide with a Mignon bulb at its tip. Already in the late 1880ies von Schrötter in Vienna developed a rigid cold light guide made of plexiglass (fig. 15) which was improved by introducing quartz by K. Storz. After Tyndalls first description of the optical properties of glass fibers in 1872, patents for glassfibers as transport medium where almost simultaneously given to Baird in England

(1926), Hansell in the US (1927) and Marconi in England (1930). The first prototype of a fiberscope was presented by Lamm in Munich (1930). After Hansen in Denmark described the first fiber bundles for light transportation in 1930, Van Heel in the Netherlands and O'Brian in the US developed the first endoscopes for bronchoscopy and gastroscopy in 1953 and 1954. The rod lens and fiberoptic lighting device by Hopkins in London were adopted by K. Storz as cold light illumination source for his rigid endoscopes in 1963. The transition to fully flexible endoscopes with image transport by glassfibers was performed by Hirschowitz and ACMI in 1958 after Curtiss of Ann Arbor had described the first medical fiber instrument in 1955.

Photo-, Film- and Videodocumentation. The first (even stereoscopic) endophotographies were performed by Czermak by use of a giant laryngeal mirror. Stein in Frankfurt used magnesia illumination for his photographic apparatus, the 'heliopictor' ca. 1875, technically the predecessor of the Polaroid-Land camera of 100 years later. Stein's camera was improved by Nitze and Kollmann. In 1907, Benda used color photography which was first introduced to bronchoscopy by P. Hollinger in 1941. Soulas (1949) and Hollinger (1956) also introduced endoscopic film documentation. The first television transmission of a bronchoscopy was performed by Dubois de Monternaud in 1955. Wittmoser constructed an angulated optic for improvement of image transfer and produced the first video documentation in 1969.

Prospect

With the advent of the flexible bronchoscope after 1966, two developments took place: bronchoscopy rapidly spread beyond otorhinolaryngological and specialized thoracic clinics, and the overall number of rigid bronchoscopies declined rapidly until the late 80ies and early 90ies because flexible bronchoscopy had become so much easier and more acceptable to the patients. But then again, the increasing number of interventional techniques demanded use of the rigid bronchoscope for safety reasons. Special rigid devices were developed by J.F. Dumon for application of the Nd:YAG laser and placement of his 'dedicated stent' and by L. Freitag for his 'dynamic stent'. Several consensus task forces, e.g. of the Scientific Section on Endoscopy of the German Society for Pulmonology and of the ERS/ATS agreed that for many interventional procedures, the bronchoscopist and staff should at least be trained in the technique of rigid bronchoscopy and should have the instrument at hand in case of an emergency. Thus, in training courses all over the world handling of the rigid instrument is taught again (fig. 16).

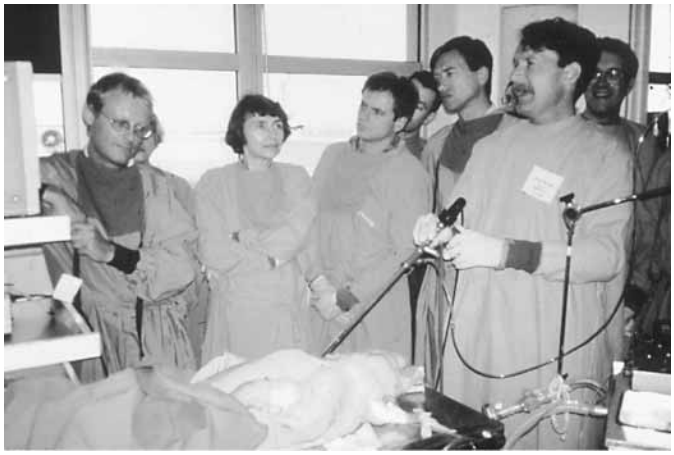

Fig. 16. Teaching rigid bronchoscopy on a pig in a training course on interventional bronchoscopy. C.T. Bolliger is demonstrating the technique to the participants while L. Freitag is watching closely.

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General Aspects of Interventional Bronchoscopy

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History of the Flexible Bronchoscope

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Summary

In the spring of 1964, Shigeto Ikeda requested Machida to produce a prototype of the first flexible bronchofiberscope, and then a similar request was made to Olympus Optical Company around the end of 1965. The first prototype flexible bronchofiberscope was completed on July 23, 1966, and delivered to him by Machida. They succeeded in the commercial production of flexible bronchofiberscopes in April, 1968. Olympus made their first prototype bronchofiberscope on August 13, 1966. Ikeda introduced and popularized flexible bronchofiberscopy throughout the world. Endoscopic examination of the tracheobronchial tree has progressed from the rigid technique originally described by Killian to flexible fiberoptics applied by Ikeda. Ikeda has also been the forerunner in the development of the videobronchoscope. With the rapid progress in electronic devices, Asahi Pentax Corp. developed a prototype videobronchoscope in February, 1987. This device offered a very clear image suitable for examination of the endoscopic image on a color screen, and, therefore, the videobronchoscope became common. Ikeda is still interested in the development of bronchoscopy in the next millennium.

Shigeto Ikeda is the inventor of the flexible bronchoscope. Nowadays, this instrument is one of the most important tools for diagnosis and treatment of pulmonary diseases.

In the endoscopic examination at that time, a small electric lamp was set at the tip of the telescope only for observation, but it was not sufficient for dynamic endoscopic image recording. To overcome this defect, a plan was made to replace the small lamp with optical glass fibers for transmission of brighter light from an outside source. In 1962, Ikeda asked the Machida Endoscope Company to produce an esophagoscopic telescope based on the above plan. A long glass fiber bundle from the grip part of the telescope was connected to a more powerful and brilliant light source to provide sufficient illumination inside the esophagus to make an esophageal motion picture. Later, he made a smaller bronchoscopic telescope with similar specifications. With this success, he obtained the idea for developing a rigid type bronchoscopic telescope with a long glass fiber bundle for illumination.

In the spring of 1964, he requested Machida to produce a prototype of the first flexible bronchofiberscope, and then a similar request was made to Olympus Optical Company around the end of 1965. In manufacturing the flexible bronchofiberscope, the most serious problem was the image resolution of the fiberoptic image bundle, and to satisfy this requirement, it was necessary to make the fiberoptic size of each optical glass fiber as thin as possible, namely the fiberoptic size of 16 μm in the gastrointestinal fiberscopes had to be reduced to 14 μm. Since 1964 starting with the first prototype, experimental production has continued, and the seventh model of the scope became the first flexible bronchofiberscope available in practice. In this way, the first prototype flexible broncho-

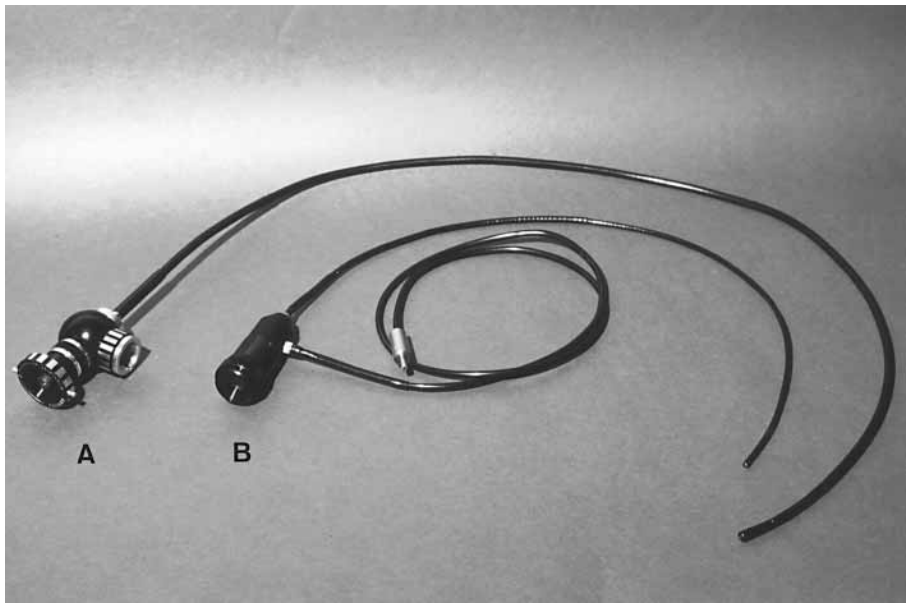

Fig. 1. Prototypes of the first flexible bronchofiberscope. A = Machida Endoscope Company; B = Olympus Optical Company.

Table 1. Specifications of Machida's bronchofiberscope

Type	Prototype 1	Prototype 3	Prototype 4	Prototype 5/6	Prototype 7
Date of manufacture	July 1966	October 1966	December 1966	March and June 1967	September 1967
Field of view	90°	80°	80°	80°	80°
Direction of view	forward viewing	forward viewing	forward viewing	forward viewing	forward viewing
Depth of field, mm	5–30	5–30	5–30	5–30	5–30
Distal end outer diameter, mm	5.0	5.0	5.0	5.0	5.0
Angulation range	no angulation mechanism	up 100° down 10°	up 150° down 10°	up 180° down 10°	up 200° down 10°

fiberscope was completed on July 23, 1966, and delivered to him by Machida (fig. 1). He attended the 9th International Congress on Diseases of the Chest in Copenhagen, Denmark, August 17–19, 1966, and presented this instrument for the first time to the world. This news was immediately transmitted and published in the New York Times, surprising the world.

After returning from Copenhagen, he made use of the first model in clinical examination and found that the following points should be considered for improvement. He found that if the scope was too flexible, it was difficult to determine when it was inserted into the bronchus, whether the scope tip was in the left lung or the right lung. The fiberscope should not be too soft, but should be slightly stiff to transmit the controlling power from the grip part to the tip. He reported the points in detail to Machida, asking for further improvements. He also found out that the image resolution was not satisfactory because of irregular alignment of the glass fiber image bundle. To make the scope insertion into the upper lobe bronchi of the left and right lungs easier, the control mechanism was built into the grip part for manipulation of the tip, the tip part was divided into two parts, apical lens and image fiber bundle, and the angle section part, which was the line of

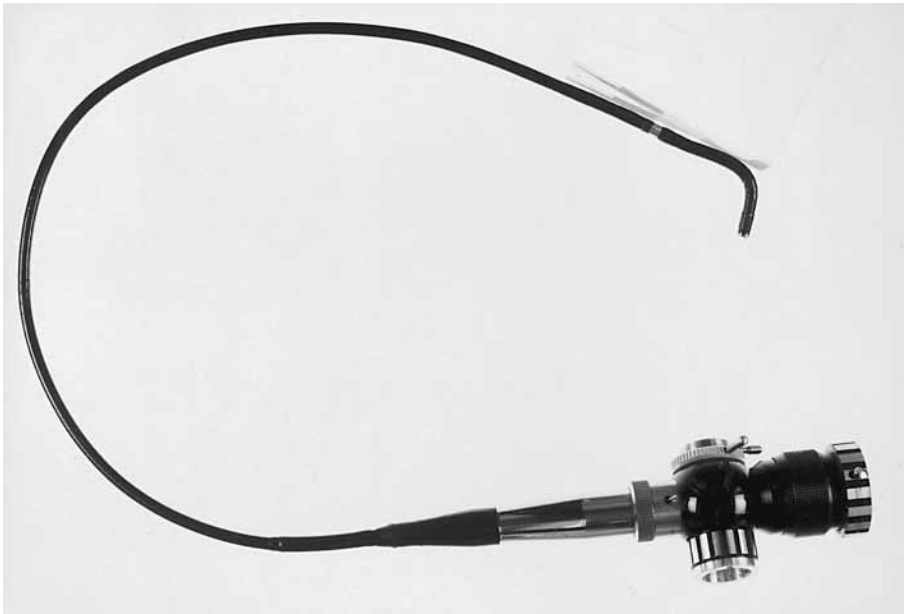

Fig. 2. The third model of the Machida bronchofiberscope.

circular rings, was connected with two wires. By pulling these wires, it became possible to make a U-turn angulation. In the seventh model of the flexible bronchofiberscope, the size and alignment of the image bundle became improved to 14 μm for each optical glass fiber, and although the rigid part, of the scope tip was shortened to only 8 mm, angulation was possible in a U turn with a built-in channel of 1 mm in the flexible part for aspiration and biopsy (table 1). They succeeded in the commercial production of flexible bronchofiberscopes in April 1968 (fig. 2, 3) [1–3]. Technical achievements stimulated the progress in gastrointestinal fiberscopes with U-turn angulation and in colonofiberscopes of smaller diameters.

Olympus made their first prototype bronchofiberscope on August 13, 1966. The first prototype had no angulation mechanism or working channel (fig. 1). They started research afterwards to develop a new method to assemble fiberoptic image bundles in a quite different manner from the conventional way.

In the autumn of 1968, Olympus commercialized three types of bronchofiberscope which proved better in handling as well as in image resolution. The popular type BF-

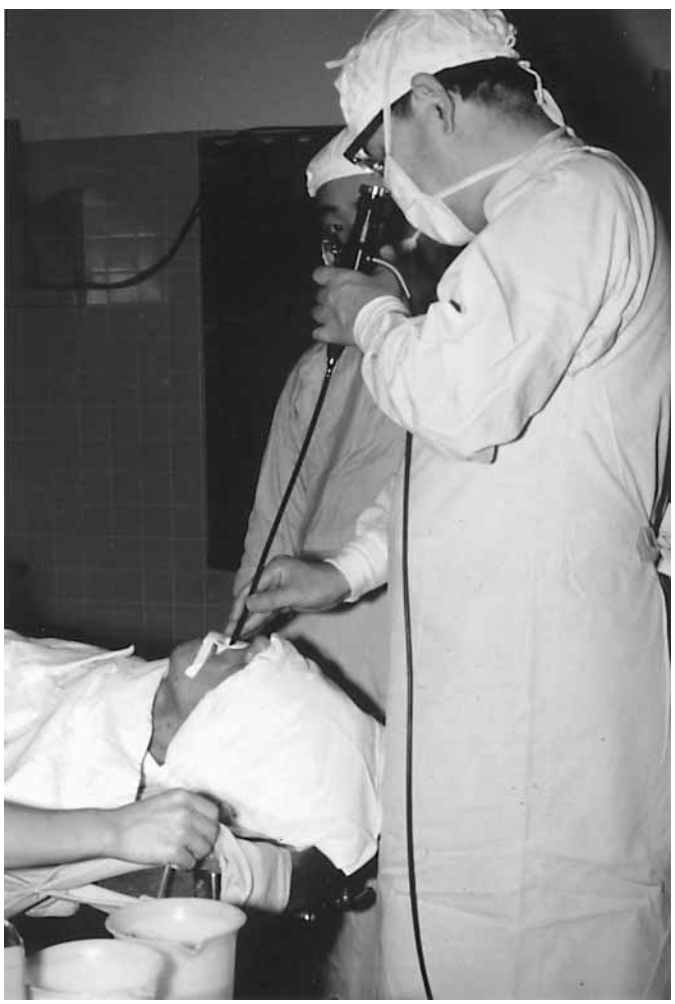

Fig. 3. Ikeda using seventh model of the Machida bronchofiberscope in a clinical examination.

Table 2. Specifications of Olympus's bronchofiberscope

Type	Prototype	BF-3A	BF-5B	BF-4B
Date of manufacture	August 1966	May 1968 (commercial)	May 1968 (commercial)	August 1968 (commercial)
Field of view	45°	66°	74°	72°
Direction of view	forward viewing	forward viewing	forward viewing	forward viewing
Depth of field, mm	5–50	3–50	5–50	3–50
Distal end outer diameter, mm	3.3	3.2	5.0	4.0
Angulation range	no angulation mechanism	up 180° down 30°	up 130° down 30°	up 160° down 30°
Working channel inner diameter, mm	no working channel	no working channel	1.4	0.6

5B had a working channel through which a cytology brush could be inserted from the channel port on the control body (table 2). Olympus had a wide sales network throughout the world, and although they started their development later than Machida, they overcame the delay in distributing the instruments throughout the world and contributed to the progress of bronchology.

In September 1968, Ikeda was invited by the National Institute of Health (NIH) in the USA and gave a lecture at the Johns Hopkins University which the staffs of NIH, Mayo Lung Project Group and American Optical Company attended. He presented a speech on the 'Flexible bronchofiberscope', showing an endoscopic motion picture using the fiberscope in the tracheobronchial tree. The audience were excited, clapping their hands and stamping their feet, when they saw the image of the fiberscope tip going into the bronchus and then into a very deep part of the bronchus. Later in October, he presented a paper concerning flexible bronchofiberscopy at the 10th International Congress on Diseases of the Chest in Washinton, D.C., with the same motion picture and attracted the attention of the participants. In 1970, he offered the technique of flexible bronchofiberscopy to the staff at Mayo Clinic (Rochester, Minn., USA). Flexible bronchofiberscopy using a double-jointed curette technique under fluoroscopic guidance was performed in patients with small peripheral lung carcinoma [4]. He introduced and popularized flexible bronchofiberscopy throughout the world. Endoscopic examination of the tracheobronchial tree has progressed from the rigid technique originally described by Killian to flexible fiberoptics applied by Ikeda [5]. In July 1978, Ikeda established the World Association for Bronchology. Also, he was elected as a Chairman of the Board of Regents of the World Association for Broncholology, and he continues in that role today.

About the year 1980, the flexible bronchofiberscope became common and its use widespread among doctors in the world. The original purpose of the flexible bronchofiberscope at the beginning was to observe lung cancer lesions in the tracheobronchial tree, to perform biopsy, curettage and brushing, so that those findings were considered for the definitive diagnosis of the case. Since the development of the equipment, however, bronchofiberscopy has been utilized not only for diagnostic but also therapeutic procedures.

Jean F. Dumon developed the Nd:YAG laser photoresection via flexible bronchofiberscopy as a preferred modality for palliative treatment of obstructive malignant tumors of the airway [6]. At the Second World Congress for Bronchology, Düsseldorf, 1980, Ikeda was impressed by Dumon's presentation 'Endoscopic fiber laser irradiation of tracheobronchial stenosis'. Immediately after that, Ikeda visited and stayed in Marseille to observe Dumon's endoscopic Nd:YAG laser surgery. Ikeda and Ryosuke Ono have applied Nd:YAG laser treatment to patients with airway stenoses since August 1980 [7]. The Nd:YAG laser equipment became common in addition to photodynamic therapy (PDT) with hematoporphyrin derivative. Yoshihiro Hayata and Harubumi Kato treated the first clinical case of early stage lung cancer by PDT with argon dye laser via flexible bronchofiberscopy in March 1980 [8]. Based on the successful results of their experimental studies, they then employed this method in human lung cancer cases. Ikeda and Ono started treating patients with roentgenographically occult lung carcinoma by PDT in July 1981 [9].

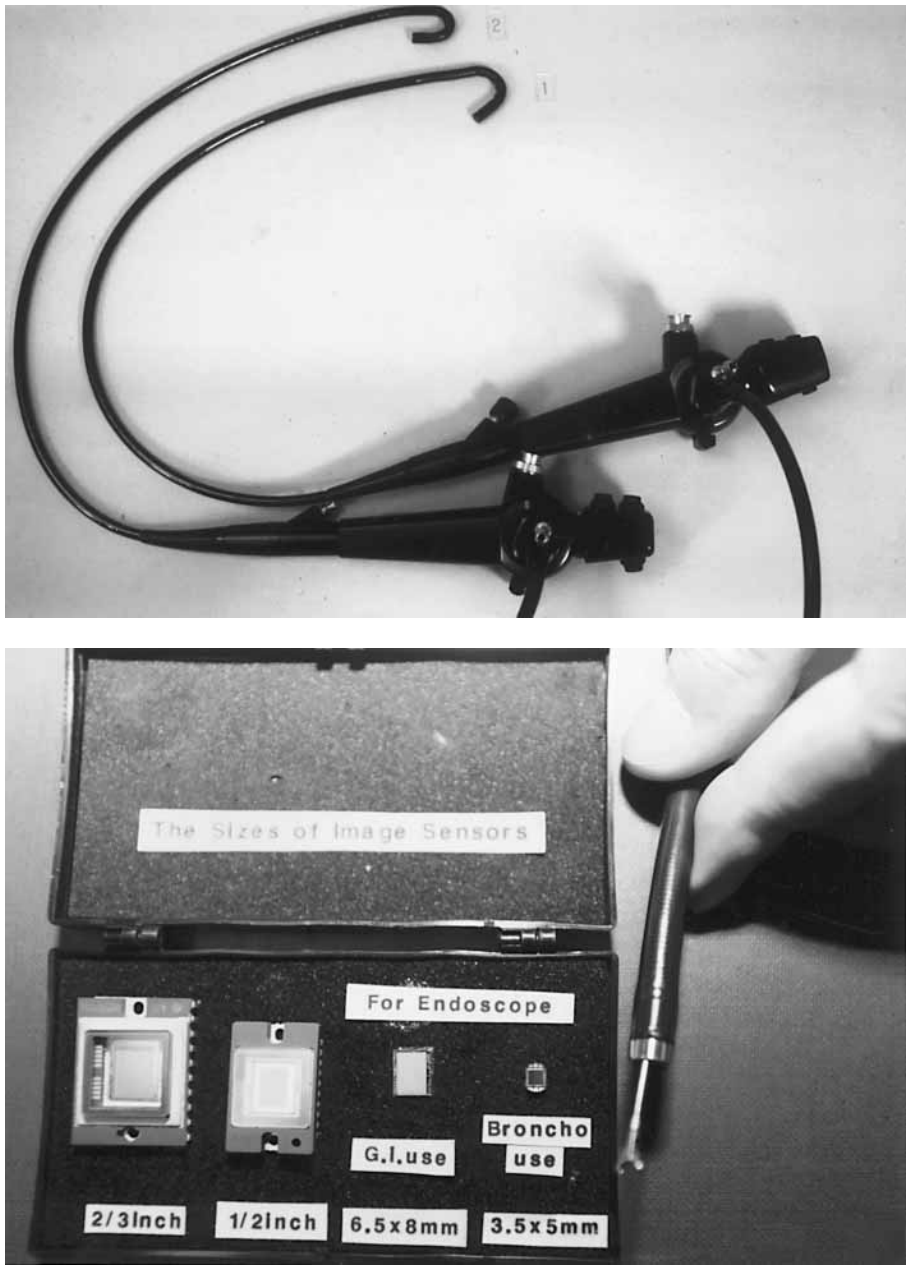

Fig. 4. **a** Prototypes of the first and second video bronchoscopes by Asahi Pentax Corp. **b** Sizes of image sensors.

Ikeda has also been the forerunner in the development of the videobronchoscope [5, 10]. With the rapid progress in electronic devices, Asahi Pentax Corp. developed a prototype videobronchoscope in February, 1987, replacing the fiberoptic image bundle with a small charge-coupled device sensor built in the tip part, which made it possible to obtain better image resolution and processing. For example, the endoscopic findings could be printed out and pasted in the patient's record file (fig. 4). With the videobronchoscope, instead of looking through the bronchofiberscope eyepiece, doctors looked at the monitor screen during the diagnostic and therapeutic procedures (fig. 5). At the end of the 1980s, a TV endoscope with a small camera at its tip, the so-called 'Videobronchoscope', was developed by Pentax, and then Olympus and Machida-Toshiba also made their models. These offered a very

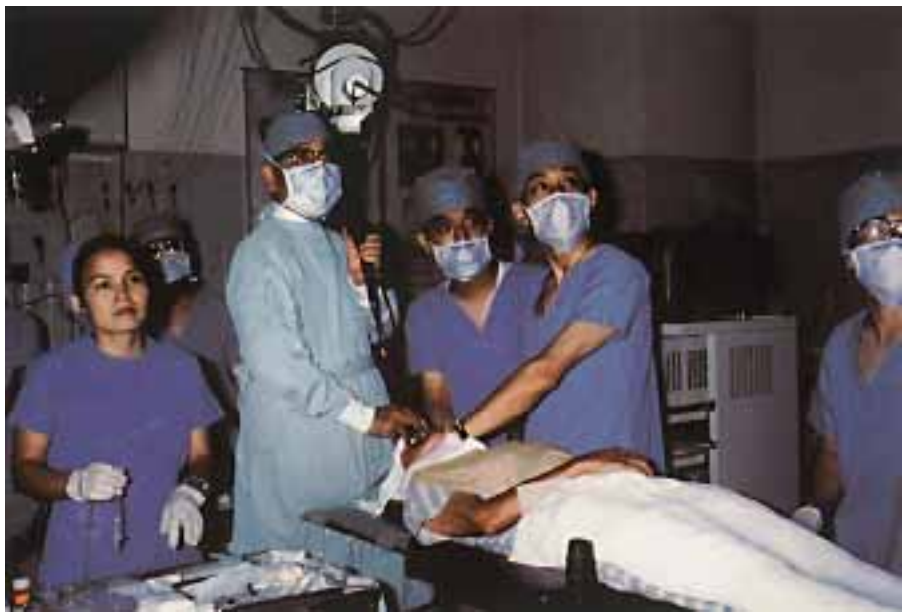

Fig. 5. Ikeda looking at the video monitor instead of looking into the bronchoscope during a procedure using videobronchoscopy.

clear image suitable for examination of the endoscopic image on a color screen, and, therefore, the videobronchoscope became common in universities and hospitals as soon as the manufacturers started commercial production. The connection of medical fiberscopes with television equipment affected the industrial applications in inspection of airplane engines and inside the public water supply tubes.

In March 1991, Ikeda retired from the National Cancer Center Hospital, Tokyo, but still is interested in the development of bronchoscopy in the next millennium, and he remains active himself. For instance, after the Tenth World Congress for Bronchology, Budapest, 1998, Ikeda visited Heinrich D. Becker at the Thoraxklinik, Heidelberg, which is a new endoscopy unit, to observe implantation of the Ultraflex stent and endobronchial ultrasound using a flexible bronchoscope.

Acknowledgment

The author thanks Dr. Shigeto Ikeda (Chair of Board of Regents, The World Association for Bronchology) for his helpful comments and data on the manuscript.

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General Aspects of Interventional Bronchoscopy

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Modern Use of Rigid Bronchoscopy

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Summary

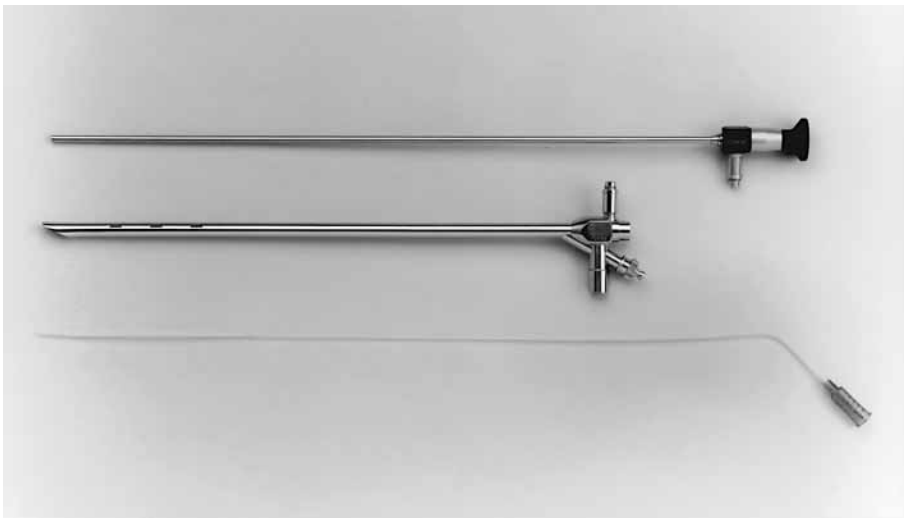
In the field of bronchoscopy, the rigid bronchoscope has both historical significance and important modern applications. A century ago, it provided physicians the first look into the lower airways; now, as in the past, its primary importance is its use as a therapeutic tool. This historic instrument has adapted extremely well to the introduction of modern therapeutic tools such as lasers, cryotherapy, electrocautery and stents. Stradeling has stated that 'no physician specializing in respiratory medicine today is considered adequately trained unless competent with the bronchoscope'. One could paraphrase Prof. Stradeling by stating that no pulmonologist specializing in bronchology today is considered adequately trained unless competent with the rigid bronchoscope. Successful rigid bronchoscopy requires expertise in flexible bronchoscopy, a certain amount of hand-eye coordination, cooperation with and support of the anesthesiologist and a well-trained bronchoscopy team. For decades, the rigid bronchoscope has been felt to be a safe and effective instrument for management of airway disorders. Modern anesthetic techniques, video technology and adjuvant therapies have only enhanced its value in the management of these disorders. The rigid bronchoscope is indeed a remarkable instrument that has truly stood the test of time. The modern rigid bronchoscopist can certainly experience the same enthusiasm for this procedure as that described by Jackson: 'The bronchi enlarge and elongate at each inspiration, diminish and shorten during expiration. The heart at each beat dings in the bronchial wall or pushes the whole bronchial tube sideways; the thumping is transmitted to the fingers holding the inserted (rigid) bronchoscope. One gets the impression of being in the midst of the machinery of life itself.' [The Life of Chevalier Jackson: An Autobiography. New York, MacMillan, 1938.]

The title of this chapter is somewhat of an oxymoron. While the rigid bronchoscope can now be used in conjunction with modern high-technology equipment, the technique of modern rigid bronchoscopy is based on time-ordered principles outlined a century ago. The introduction of the flexible bronchoscope 30 years ago and the almost simultaneous beginning of the epidemic of lung cancer revolutionized the field of bronchoscopy. The flexible bronchoscope has become the standard instrument for diagnostic bronchoscopy, and is a most valuable tool for many therapeutic procedures.

The rigid bronchoscope was the sole instrument to access the airway from its introduction by Killian in 1897 until the flexible bronchoscope was developed in the late 1960s. Although its use has diminished in numbers, rigid bronchoscopy is not a 'forgotten art' as suggested by some. Modern interventional procedures such as laser bronchoscopy, stent insertion, cryotherapy and electrocautery have rekindled interest in rigid bronchoscopy among physicians who felt that the instrument had only limited indications, and has reinforced the importance of the procedure among physicians who were already familiar with the instrument. Once a procedure only performed by surgeons, it is now a procedure commonly performed by interventional pulmonologists.

Historical Background

Gustav Killian, Professor of Otolaryngology at the University of Freiburg, Germany, is considered the 'Father of Bronchoscopy' [1]. He performed the first translaryngeal rigid bronchoscopy in 1887, and quickly became world-famous for his expertise in removing foreign bodies from the airway. One of his American pupils, Chevalier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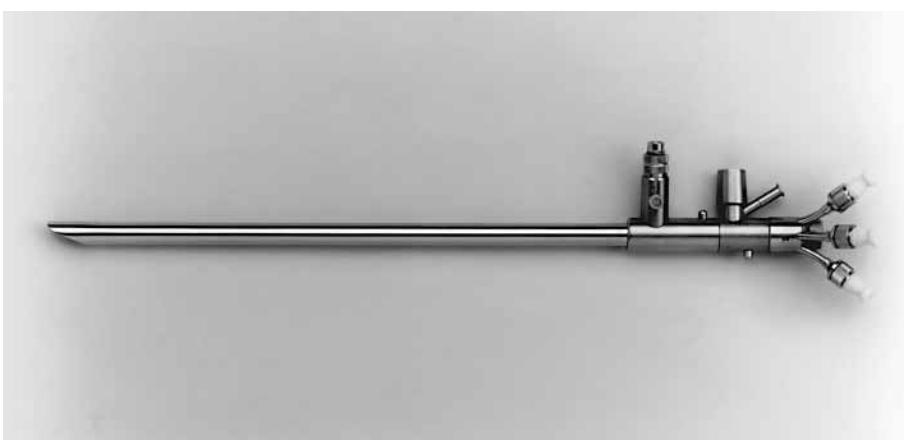
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Fig. 1. **a** Modern rigid bronchoscope (middle) with telescope and semirigid suction catheter. **b** Operating end of bronchoscope with telescope and suction catheter in place. **c** A tracheoscope with end caps that allow insertion of laser fiber and suction catheter.

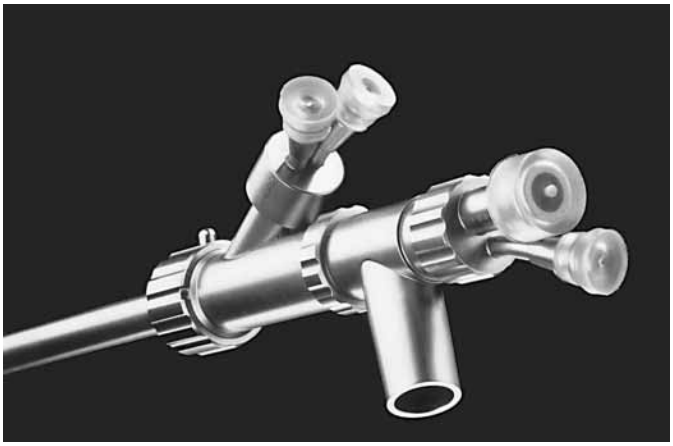

Fig. 2. Proximal end of universal head of Dumon bronchoscope showing ports for suction catheters, laser fiber, telescope and ventilation.

Jackson, made many further advances in rigid bronchoscopy technique and equipment [2]. Jackson, also an otolaryngologist, was a superb clinician, a tool designer and maker, and an excellent medical artist. He made many improvements to the bronchoscope and accessory equipment. Through his lectures, books, illustrations and training programs in Philadelphia medical schools, he fostered a whole generation of American and international bronchoscopists. The legacy of Killian and Jackson forms the basis of modern rigid bronchoscopy practice.

The Instrument

The modern rigid bronchoscope (fig. 1) is a straight, hollow metal tube usually with a uniform diameter throughout its length and is quite similar to that designed by Jackson nearly a century ago. The lumen shape is close to circular, and the wall thickness is 2–3 mm. Adult bronchoscopes range in diameter from 9 to 13.5 mm and are approximately 40 cm in length. The distal end is beveled, which permits easier passage through the vocal cords and across areas of stenosis. The beveled edge also serves as a chisel allowing resection of tumor from the airway wall. The distal one third of a bronchoscope barrel contains openings that permit ventilation of the opposite lung if the tube is passed deep into the airway on one side. A tracheoscope, on the other hand, is a shorter instrument which is similar to the bronchoscope except that there are no side holes on the barrel.

The operator end of the bronchoscope may contain several ports. The open end can be capped or can allow passage of telescopes or other instruments. A large side port usually comes off at 90° and can be connected to an anesthesia apparatus or can be left open to entrain room air. Often there is also an angled side port which can receive suction catheters or can be connected to ventilating equipment for use with Venturi Jet ventilation (fig. 1).

A new bronchoscope designed by Dumon (Efer Company, LaCiotot, France; Bryan Corporation, Woburn, Mass., USA) is the first major redesign of the rigid bronchoscope since the Jackson era (fig. 2). The bronchoscope consists of a universal head, which has an open end and has side ports for the anesthesia apparatus and for instrument and suction equipment. Multiple bronchoscope barrels ranging from pediatric size to adult (largest 13.5 mm OD) can be attached to this head. Similar sized tracheoscopes are also available. An introducer system for silicon stents is designed specifically for this bronchoscope. Rigid bronchoscopes specifically designed for laser use have been marketed recently [3, 4]. These offer little advantage over standard rigid bronchoscopes.

The pioneers of rigid bronchoscopy were required to visualize the airways by looking directly down the inner barrel of the bronchoscope with monocular vision aided by reflected light. Modern rigid bronchoscopes have light carriers incorporated into the wall of the scope which provide adequate visualization for intubation, suctioning or removal of foreign bodies or tumor tissue. However, the excellent views of the airway associated with modern rigid bronchoscopy rely on the use of optical telescopes which are passed through the bronchoscope. These deliver bright light to the airway and provide a magnified wide-angled view of the airway lumen. The telescope can be connected to a CCD chip camera, thus allowing the entire bronchoscopy team to visualize the procedure on a video monitor and permitting video recording. Many other ancillary instruments, including biopsy forceps, alligator forceps, foreign body retrieval instruments and rigid and semirigid suction catheters can also be placed down the barrel of the bronchoscope [5].

Indications for Rigid Bronchoscopy

For nearly seven decades, the rigid bronchoscope was the sole instrument available for diagnostic and therapeutic procedures on the airway. In the last 30 years, the flexible bronchoscope has become the instrument of choice for nearly all diagnostic airway procedures and also has proven useful for many therapeutic uses. However, the rigid bronchoscope remains an important instrument

primarily for therapeutic procedures including laser bronchoscopy, cryotherapy, electrocautery, foreign body removal, stent insertion and dilatation of stenosis [5–8]. Table 1 lists current indications for rigid bronchoscopy. Many of these procedures are discussed in detail in other chapters of this monograph. In general terms, the main indications for rigid bronchoscopy involve foreign body removal, relief of malignant airway obstruction, management of massive hemoptysis and pediatric bronchoscopy. The need for deep bronchial biopsy with the rigid bronchoscope has been obviated with the wider application of transbronchial needle aspiration for diagnosis of submucosal and mucosal lesions.

Table 1. Current indications for rigid bronchoscopy

Diagnostic
Deep biopsy
Photographic documentation
Pediatric bronchoscopy
Therapeutic
Massive hemoptysis
Dilation of stenosis
Laser therapy
Stent insertion
Foreign body removal
Tumor resection
Cryotherapy
Electrocautery

Adapted from [7].

Foreign Body Removal

Foreign body removal was the initial indication for rigid bronchoscopy, as performed by Killian and Jackson. Today, foreign body aspiration is an uncommon event and is often considered as an amusing anecdote. Because of familiarity with the flexible bronchoscope, many physicians initially attempt foreign body removal with it using various accessory instruments such as biopsy forceps and basket snares. Proponents of flexible bronchoscopy use for foreign body removal emphasize that the procedure can be performed under topical anesthesia and that more distal foreign bodies can be retrieved. Rigid bronchoscopy, however, remains the preferred technique for removing large, central foreign bodies. Although the procedure requires general anesthesia, it is often quicker and it assures control of the airway as the foreign body is removed. Mehta and Dasgupta [9] and Diaz-Jimenez [10] have recently debated the merits of rigid and flexible bronchoscopy for foreign body removal.

Malignant Airway Obstruction

In the last two decades, central airway obstruction from carcinoma of the lung and other malignancies has become a common clinical problem encountered by pulmonologists. A less common cause of central airway obstruction is benign stenosis, either idiopathic, iatrogenic or posttraumatic. These conditions can often be effectively treated with methods that employ the rigid bronchoscope. Mathisen and Grillo [11] have reaffirmed the time honored technique of 'coring out' obstructing airway neoplasms with the rigid bronchoscope. These authors feel that palliation of symptoms and establishment of an adequate airway can be carried out effectively with the rigid bronchoscope alone. Many other authors, however, appreciate the advantages of adjunctive therapies such as laser [12], electrocautery [13], cryotherapy [14] or other techniques that either ablate tumor or provide photocoagulation of the tumor's blood supply. Most modern rigid bronchoscopists feel that tumors can be more safely resected with less chance of hemorrhage if one of these techniques is employed prior to resection. The large-diameter barrel of the rigid bronchoscope easily allows use of these adjunctive techniques. Once the vascular supply of the tumor has been reduced, large pieces of tumor can be removed through the barrel of the bronchoscope with various suction or grasping tools.

The placement of silicon endotracheal and endobronchial stents in the management of malignant and benign central airway obstruction mandates the use of the rigid bronchoscope. Straight silicon tubes can be either placed over a rigid bronchoscope, folded within a bronchoscope, or placed inside dedicated delivery tubes and then released into the airway with the rigid bronchoscope [15, 16]. Y stents for bilateral mainstem obstruction and pericarinal pathology require the use of the rigid instrument [17]. Attempts have been made to insert silicon stents with a flexible bronchoscope, but these techniques are cumbersome, time-consuming and likely to result in improper placement when compared to rigid bronchoscope insertion.

Hemoptysis

The role of bronchoscopy in management of massive hemoptysis continues to be controversial. Many bronchoscopists first approach patients with massive hemoptysis using the flexible bronchoscope. However, the rigid bronchoscope remains the classic instrument for bron-

Table 2. American society of anesthesiologists classification of physical status [25]

Class	Description
Class I	A normal healthy patient
Class II	A patient with mild systemic disease
Class III	A patient with severe systemic disease that limits activity but is not incapacitating
Class IV	A patient with an incapacitating systemic disease that is a constant threat to life
Class V	A moribund patient not expected to survive 24 h with or without operation
E	In the event of an emergency operation, precede the number with an 'E'

choscopy in patients with copious airway bleeding. The rigid bronchoscope provides safe ventilation, use of large suction catheters for removal of blood and clot, and the ability to tamponade bleeding central lesions. Techniques that provide photocoagulation of visible lesions such as electrocautery and laser can be used through the rigid bronchoscope. The flexible bronchoscope can be passed through the rigid bronchoscope once the airway is cleared of blood in order to visualize more distal lesions [18].

Pediatric Bronchoscopy

As in the case of bronchoscopy in adults, the flexible bronchoscope is becoming more widely used in pediatric bronchoscopy [19, 20]. Godfrey et al. [21] and Wiseman et al. [22], however, have recently presented large series of pediatric patients undergoing rigid bronchoscopy and emphasize the continued utility of this technique. The procedure can be carried out with low morbidity in infants and children, results in high diagnostic yields and also provides the ability to perform therapeutic interventions. There is no doubt that the future will result in increasing use of flexible bronchoscopy in children; however, the rigid bronchoscope continues to be an important tool in the management of pediatric airway disease [23].

Contraindications

Similar to flexible bronchoscopy, there are very few contraindications to rigid bronchoscopy. Since most patients undergoing rigid bronchoscopy require general anesthesia, the common contraindications to anesthetic agents such as unstable cardiovascular status, life-threatening cardiac arrhythmias or respiratory failure with refractory hypoxemia would prohibit the use of the rigid bronchoscope. A patient with an unstable cervical spine or diminished range of motion of the cervical spine caused by spondylosis should not undergo rigid bronchoscopy, as excessive motion of the neck during the procedure may be dangerous. Patients with maxillofacial trauma or any head and neck condition that prevents opening of the jaw to admit the bronchoscope are best examined with the flexible bronchoscope. Laryngeal stenosis or obstructing laryngeal carcinoma may prevent the translaryngeal passage of the bronchoscope. Possibly the most important contraindication to rigid bronchoscopy is an inexperienced or inadequately trained bronchoscopist, anesthesiologist or bronchoscopy team.

Complications

Severe complications from rigid bronchoscopy should be rare. Caputi et al. [24] reported only two deaths in over 11,000 rigid bronchoscopies at their center in Naples. This group divided complications into those caused by preoperative and anesthetic agents, complications due to the introduction and presence of the bronchoscope within the airway and complications caused by various biopsy procedures. Cardiac arrhythmias and ischemia are potentially the most dangerous complications, and are often related to the development of hypoxemia during the procedure. Injury to the teeth, gums and larynx is possible, especially in patients with short, thick necks and micro-agnathia. Rupture of the tracheal or bronchial wall has been reported and is always of concern when aggressive dilation or tumor resection is carried out. Fortunately, complications are rare and can be avoided by using the proper technique described many years ago by Killian and Jackson, complemented by modern anesthetic agents and monitoring techniques.

Technique

Patient Preparation

Since most rigid bronchoscopy procedures are performed in an operating room setting, standard preoperative assessment and anesthesia evaluation should be carried out. The anesthesiologist should meet the patient preoperatively and outline the technique and risks of anesthesia. In the US, patients are categorized for risk using the American Society of Anesthesiologists Classification of Physical Status (table 2) [25]. Preoperative laboratory

testing is determined by the patient's condition, age, perceived risk and hospital requirements. Careful evaluation of the oral cavity, teeth, and jaw and neck mobility should be made.

Anesthesia

The bronchoscopist must have excellent communication with the anesthesiologist. Both consider the airway exclusive territory, but in the case of bronchoscopy, they must learn to share both the locale and the responsibility of the procedure. Standard anesthetic monitoring should include pulse oximetry, electrocardiographic and blood pressure monitoring, and some attempt at monitoring of ventilation. This might include end tidal CO_2 monitoring when a closed system is employed or simple observation of chest wall excursion with an open system and jet ventilation.

Detailed description of anesthesia for rigid bronchoscopy is beyond the scope of this chapter. Originally, rigid bronchoscopy was performed using topical anesthesia and minimal sedation. This often resulted in much discomfort for the patient. Modern rigid bronchoscopy is almost universally carried out under general anesthesia (table 3). Occasionally, patients can be bronchoscoped using topical lidocaine anesthesia and intravenous conscious sedation. Intravenous propofol is the preferred agent for rigid bronchoscopy at this time. This agent produces rapid onset of anesthesia and permits rapid reawakening. Propofol does not have ideal amnesic or analgesic properties, therefore preoperative use of an anxiolytic and amnestic agent such as midazolam is recommended. Intermittent boluses of an intravenous narcotic such as fentanyl often reduce the propofol requirements and treat any acute pain experienced during the procedure.

Ventilation

Multiple options exist for ventilating a patient during rigid bronchoscopy. Ideally, the patient should be allowed to breathe spontaneously while being at a plane of anesthesia that provides comfort as the bronchoscope is passed. Often this is not possible or is insufficient to suppress cough during delicate manipulations within the airway. Spontaneous/assisted ventilation, as described by Perrin et al. [26], provides deeper anesthesia to the point where spontaneous ventilation, although preserved, is quite shallow. Frequent assisted breaths must be provided by the anesthesiologist. This method leads to rapid reawakening after the procedure, but is often insufficient to control cough. Performing rigid bronchoscopy during apnea after breathing 100% oxygen may provide sufficient time for an expert to perform a short procedure, such as removal of a foreign body, but it is usually not appropriate for most indications.

Table 3. Ventilation and anesthesia for rigid bronchoscopy [7]

Ventilation options
Apnea
Spontaneous
Spontaneous/assisted
Controlled
Closed system
Open system – jet ventilation
Via endotracheal tube
Anesthetic techniques
Topical/sedation
General
Inhalational
Intravenous

Modern rigid bronchoscopy involving use of lasers or other interventional techniques requires longer procedure times which are often facilitated by controlled ventilation [27]. Controlled ventilation with a closed system requires capping of the proximal end of the bronchoscope and any small side ports and connecting the large side port to an anesthesia machine. Some method of preventing air leaking through the vocal cords must be provided. A totally closed system allows the use of inhalational anesthetics. Another method of closed ventilation involves placing a small endotracheal tube through the larynx to ventilate the patient, and then passing the rigid bronchoscope alongside the endotracheal tube. The size of the larynx limits the diameter of the rigid tube that can be used with this technique. Venturi jet ventilation permits the use of an open system and has been shown to maintain effective gas exchange during long procedures. Godde et al. [28] have described the Venturi jet technique, which involves injecting 100% oxygen at 50 psi into the side port of the bronchoscope. Adequacy of ventilation is determined by observing movement of the chest with each injected breath. Since room air is entrained through the open end of the bronchoscope, the exact fraction of inspired oxygen is unknown. Oxygenation is monitored with pulse oximetry. Providing 10–20 breaths per minute with this technique, which often requires the use of muscle relaxants, results in adequate ventilation. The Venturi technique can also be used with high-frequency ventilation using rates up to 100 per minute [29].

Since bronchoscopy is considered a clean but not a sterile procedure, bronchoscopists classically have worn gloves, a mask and a standard short-sleeve operating scrub suit. However, in this era of universal precautions, when there is potential risk from contact with bodily secretions, it is prudent for the bronchoscopist to wear a full operating gown, glasses or other eye protection equipment, and an approved facial mask that limits inhalation of laser plume and aerosolized infectious agents (fig. 3).

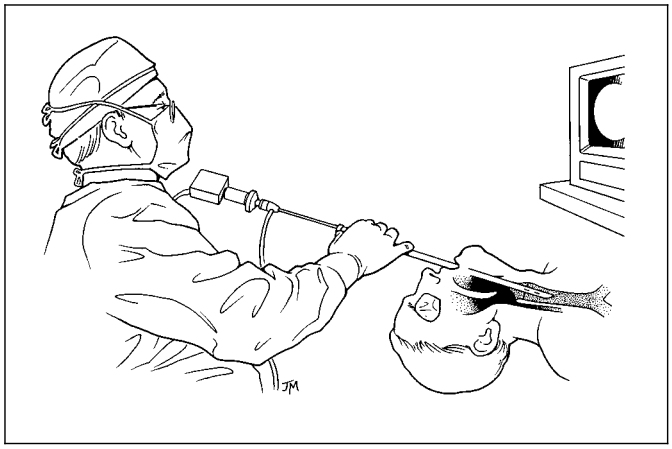

Fig. 3. Bronchoscopist, properly gowned, performing a procedure using a video monitor.

Insertion Techniques

There are several methods of insertion of the rigid bronchoscope. The method chosen depends on the expertise of the bronchoscopist and the patient's anatomy and clinical status and on discussion with the anesthesiologist. There are a number of detailed reviews of various rigid bronchoscopy insertion techniques both classic [30] and modern [5–7, 31]. Some of the techniques will be summarized below. All begin with the patient pre-medicated, well oxygenated and comfortably lying supine on the operating table. A general anesthetic is administered and muscle relaxants, if needed, are infused. A disposable tooth guard is placed on the upper teeth and the patient's eyes are protected. The bronchoscopist then chooses one of the following methods.

Classic Technique

The left thumb is placed over the upper teeth and the left index finger is placed in the mouth protecting the lower teeth and opening the jaw. The bronchoscope is held in the right hand with the bevel anteriorly (fig. 4). The bronchoscope is passed perpendicular to the table exactly in the midline. Once the uvula is passed, the right hand lowers the operator end of the bronchoscope and the base of the tongue is gently raised. The epiglottis usually comes into view at this point. The bevel of the bronchoscope is used to carefully raise the epiglottis bringing the larynx and vocal cords into view. At this point, the bronchoscope is turned 90° to the side and advanced through the vocal cords. Once the scope is passed into the trachea, the bronchoscope is then turned back 90° so that the bevel is again anterior. Using a gentle twisting motion and holding the barrel of the bronchoscope with the fingers of the left hand in a fashion similar to holding a pool cue, the bronchoscope is advanced into the lower airways.

Introduction Using a Laryngoscope

With this technique, a straight laryngoscope is used to visualize the epiglottis (fig. 5). Once the epiglottis comes into view, the laryngoscope blade is used to lift the base of the tongue raising the epiglottis slightly. With the right hand holding the bronchoscope, the tip of the scope is passed just under the epiglottis. At this point, the bronchoscopist looks through the bronchoscope and guides the bronchoscope toward the larynx and simultaneously removes the laryngoscope. The vocal cords are passed in a manner similar to that of the classic technique.

Intubation Insertion along an Endotracheal Tube

Many patients requiring interventional bronchoscopy procedures have developed respiratory failure and come to the bronchoscopy suite intubated receiving mechanical ventilation. After general anesthesia is administered, the bronchoscope can be passed along the endotracheal tube from the right side of the mouth. The bronchoscope is kept slightly anterior to the endotracheal tube and advanced under the epiglottis to the point where both the left and right vocal cords can be visualized. At this point the anesthesiologist releases the endotracheal balloon cuff and slowly pulls out the endotracheal tube. Once the tip of the endotracheal tube passes through the vocal cords, the bronchoscope is rotated 90° and quickly advanced through the cords.

This approach is recommended for any novice rigid bronchoscopist. Nonintubated patients coming into the operating room can be intubated by the anesthesiologist after induction of general anesthesia and muscle relaxation. The bronchoscopist can then advance the bronchoscope to the level of the vocal cords in an unhurried pace knowing that oxygenation and ventilation will be maintained.

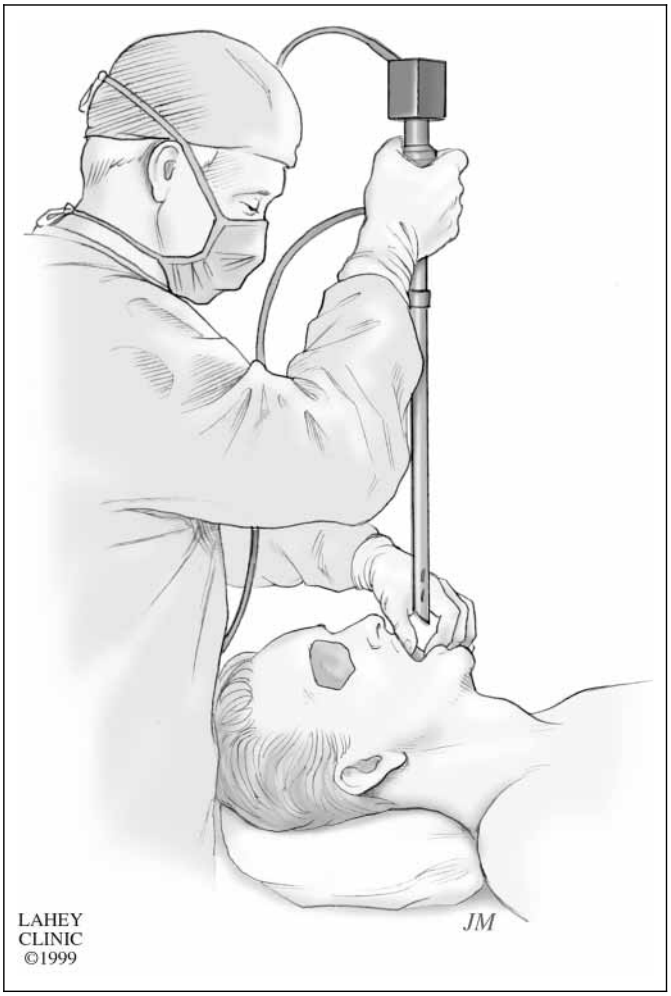

Fig. 4. Initial position of bronchoscopist, patient and bronchoscope for the classic insertion technique.

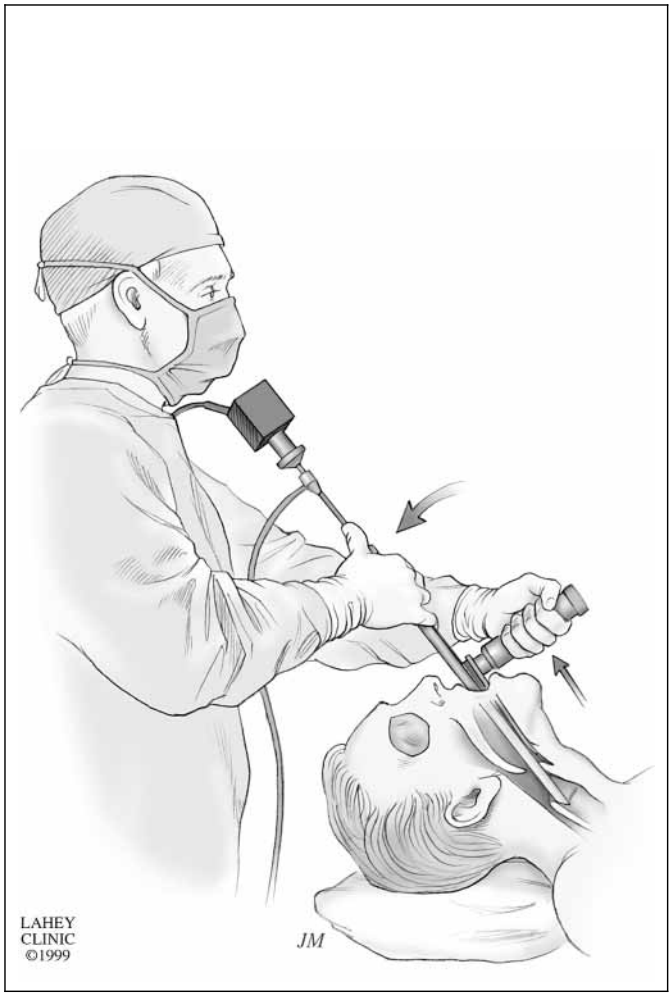

Fig. 5. Insertion of rigid bronchoscope using a laryngoscope. The laryngoscope was used to expose and lift the epiglottis and is removed as the bronchoscope is guided through the larynx.

Bronchoscopic Insertion through Laryngectomy Stoma

In this situation, a tracheoscope is preferred. The patient's neck is turned to one side and the tracheoscope is then inserted through the tracheostomy stoma. This procedure can often be carried out with topical lidocaine anesthesia and mild intravenous sedation. Muscle relaxation is rarely required.

Once the bronchoscope passes the midtracheal level, the remainder of the procedure is similar for all intubation techniques. To enter the right bronchial tree, the patient's head is turned to the left and the bronchoscope gently advanced past the carina in a twisting manner. The rigid bronchoscope can be easily passed into the distal bronchus intermedius in most patients. To enter the left bronchial tree, the patient's head is turned toward the right shoulder and again the bronchoscope is advanced in a twisting motion. Unless there is major distortion of the anatomy related to past surgery or radiation therapy, the left upper and left lower lobe bronchi can be visualized in most patients.

Removal of the bronchoscope from the airway should always be done visually, again using a gentle twisting motion. Patients are usually observed in a recovery area for several hours after the procedure. Because the effects of modern intravenous anesthetic agents and muscle relaxants resolve quickly, rigid bronchoscopy can often be performed on an outpatient basis [32]. The patient's overall condition and not the procedure determine the need for hospital admission.

Training for Rigid Bronchoscopy

In many European centers training in rigid bronchoscopy is an integral part of pulmonary fellowship training. This is not the case in the US and Japan, where rigid bronchoscopy remains an uncommon, sometimes forgotten procedure performed by less than 10% of bronchoscopists. In these countries achieving training in rigid bronchoscopy is often difficult as experience with the procedure is not a requirement of current pulmonary and critical care medicine fellowships, and access to rigid bronchoscopic equipment and operating room privileges may be difficult to obtain. Years ago, Jackson emphasized that rigid bronchoscopy is 'not an undergraduate subject'. It is advisable that one have extensive experience in flexible bronchoscopy before attempting to use the rigid instrument. Jackson also states that 'a fundamental knowledge of technique, positions, and landmarks is necessary, after which only continued manual practice is needed for proficiency'. Fortunately there are now a number of postgraduate courses during which experienced thoracic endoscopists can at least achieve a rudimentary knowledge of rigid bronchoscopy technique. These courses often include practice on animal models and intubation mannequins. Following this initial experience, practice on humans under the guidance of an expert should allow most serious thoracic endoscopists enough experience to eventually perform the procedure alone.

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Bronchoscopy Unit, Expertise, Equipment and Personnel

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Summary

A special unit dedicated to bronchoscopy and related procedures may not be practical at all medical centers. However, comprehensive practice of interventional pulmonology will require a dedicated unit where a large number of specialized bronchoscopy procedures such as special bronchoscopies, laser therapy, stent placement, pediatric bronchoscopy, complicated rigid bronchoscopy, thoracoscopy, transthoracic needle aspiration of pulmonary centers and percutaneous tracheostomy are performed on a regular basis. The major advantages of a dedicated bronchoscopy unit are the availability of any type of instrument and the facility to perform all types of bronchoscopy-related procedures. Certain procedures, for example bronchoscopic lung biopsy under fluoroscopy, may necessitate the use of the radiology suite, if a mobile fluoroscope is not available. The need for a dedicated bronchoscopy unit should be determined by the number of procedures performed in a given time period at any medical center as well as the expertise of physicians who practice bronchoscopy and related procedures. A dedicated bronchoscopy unit consists of a predefined physical location where the procedures are performed, all equipment necessary to provide bronchoscopy and related procedures, facilities to administer general anesthesia, immediately available pathology services, and a bronchoscopy team composed of well-trained bronchologists, anesthesiologists, and nurses/surgical technicians. It is important to recognize that an overwhelming number of 'routine' bronchoscopy procedures can be performed safely in other areas, including the patient's room, intensive care unit, emergency ward and in an outpatient setting. Therefore, the bronchoscopy team should be mobile enough to perform bronchoscopy procedures in almost any location within the medical center at a short notice. Irrespective of the location where the procedure is performed, the basic maxim is that the bronchoscopy team is optimally trained to perform the procedure and handle complications.

Bronchoscopy and related procedures are commonly performed in most medical centers that provide tertiary medical care. The sheer number of procedures performed in such medical centers necessitates organization and maintenance of a devoted bronchoscopy suite or unit. However, a special unit dedicated to bronchoscopy and related procedures may be impractical at all medical centers. The need for a dedicated bronchoscopy unit is dependent on the overall medical care provided by the medical center and the types of bronchoscopy services practiced, such as special bronchoscopies, laser therapy, stent placement, pediatric bronchoscopy and complicated rigid bronchoscopy. The last decade has witnessed growth of departments specializing in interventional pulmonology in which not only bronchoscopy but also other procedures such as thoracoscopy, transthoracic needle aspiration and percutaneous tracheostomy are performed on a

regular basis. Therefore, comprehensive practice of interventional pulmonology will require a dedicated unit for smooth performance of these procedures. Most importantly, the need for a dedicated bronchoscopy unit is dictated by the number of bronchoscopy procedures performed in a given time period at any medical center as well as the expertise of physicians who practice bronchoscopy and related procedures.

A dedicated bronchoscopy unit consists of not only a predefined physical location where the procedures are regularly performed, but also readily available equipment necessary to provide bronchoscopy and related procedures, and a team composed of well-trained bronchologists, anesthesiologists and nurses/surgical technicians. While it is convenient to have a dedicated operating room or other facility, an overwhelming number of 'routine' bronchoscopy procedures can be performed safely in other areas, including the patient's room, intensive care unit, emergency ward and in an outpatient setting. Thus, a dedicated bronchoscopy unit cannot be stationary. The bronchoscopy service should be mobile enough to perform bronchoscopy procedures in almost any location within the medical center at a short notice. Irrespective of the location where the procedure is performed, the fundamental tenet is that the bronchoscopy team is optimally trained to perform the procedure, and it includes the personnel and equipment to deal with complications, should they develop [1, 2].

Certain procedures require specific amenities to enable the bronchologist to provide optimal bronchoscopy services. For instance, bronchoscopic lung biopsy under fluoroscopy may call for using the radiology suite, if a mobile fluoroscope is not available. Another example is where the laser bronchoscopy has to be performed in a laser unit located in a separate area, away from the location where routine bronchoscopies are done. As indicated above, a patient in the intensive care unit may require bedside bronchoscopy. This necessitates the availability of a mobile bronchoscopy unit. At major medical centers with busy practice of thoracic surgery, it is a common practice to perform intraoperative bronchoscopy to assist the thoracic surgeon [3]. This requires the availability of the bronchoscopist and bronchoscopy equipment in the operating room. Before the introduction of the flexible bronchoscope into clinical practice, evaluation of the tracheobronchial tree of infants required transportation to the operating room for rigid bronchoscopy. Presently, however, the availability of the small-diameter (ultrathin) flexible bronchoscope allows safe performance of bronchoscopy in the neonatal intensive care unit [4, 5]. Nevertheless, rigid bronchoscopy can be performed in the neonatal intensive care unit, provided appropriate equipment and personnel are available [2, 6].

The American College of Chest Physicians (ACCP) survey, in 1989, of 871 bronchoscopists in the US and Canada revealed that bronchoscopy was performed in various physical locations: the operating room (50%), patient's room (56%), physician's office (11%), in a bronchoscopy suite/laboratory or pulmonary function test laboratory (17%) and intensive care unit (2.5%) [7]. Outpatient bronchoscopy (in the hospital) was practiced by 63% of physicians. A more recent postal survey by the American Association for Bronchology (AAB) in 1999 elicited responses from 744 of the 3,000 North American bronchologists who received the questionnaire, and of the respondents, only 28% indicated that they had a dedicated unit for bronchoscopy, which was also used as the postbronchoscopy recovery area [8]. In 1995, the pediatric bronchology group of the European Respiratory Society surveyed 125 European medical centers, of whom 51 (41%) responded. The survey observed that flexible bronchoscopy was carried out in the operating room in 19 centers, in the intensive care unit in 22 centers and in specially equipped rooms in 30 centers, whereas the rigid bronchoscopy was performed in the operating room in 23 centers, in the intensive care unit in 7 centers and in a equipped room in 15 centers [9].

The Bronchoscopy Unit

The physical requirements of an ideal bronchoscopy unit include adequate space for the following: Storage of bronchoscopy-relaetd equipment, prebronchoscopy preparation of the patient, performance of the procedure and a postbronchoscopy area to observe the patient. As indicated by the surveys by the ACCP and the AAB, this ideal is far from reality in North America [1]. The dimensions of the bronchoscopy unit will depend on the types of procedures performed and the daily case load of each bronchoscopist and medical center. The major advantages of a dedicated bronchoscopy unit are the availability of any type of instrument and the facility to perform all types of bronchoscopy-related procedures. At medical centers which perform a significant number of complicated bronchoscopic procedures such as laser bronchoscopy, stent placement, pediatric bronchoscopy and complicated rigid bronchoscopy, it may be convenient to locate the bronchoscopy unit adjacent to surgical operating rooms so that the expertise of the thoracic surgeons and the anesthesiol-

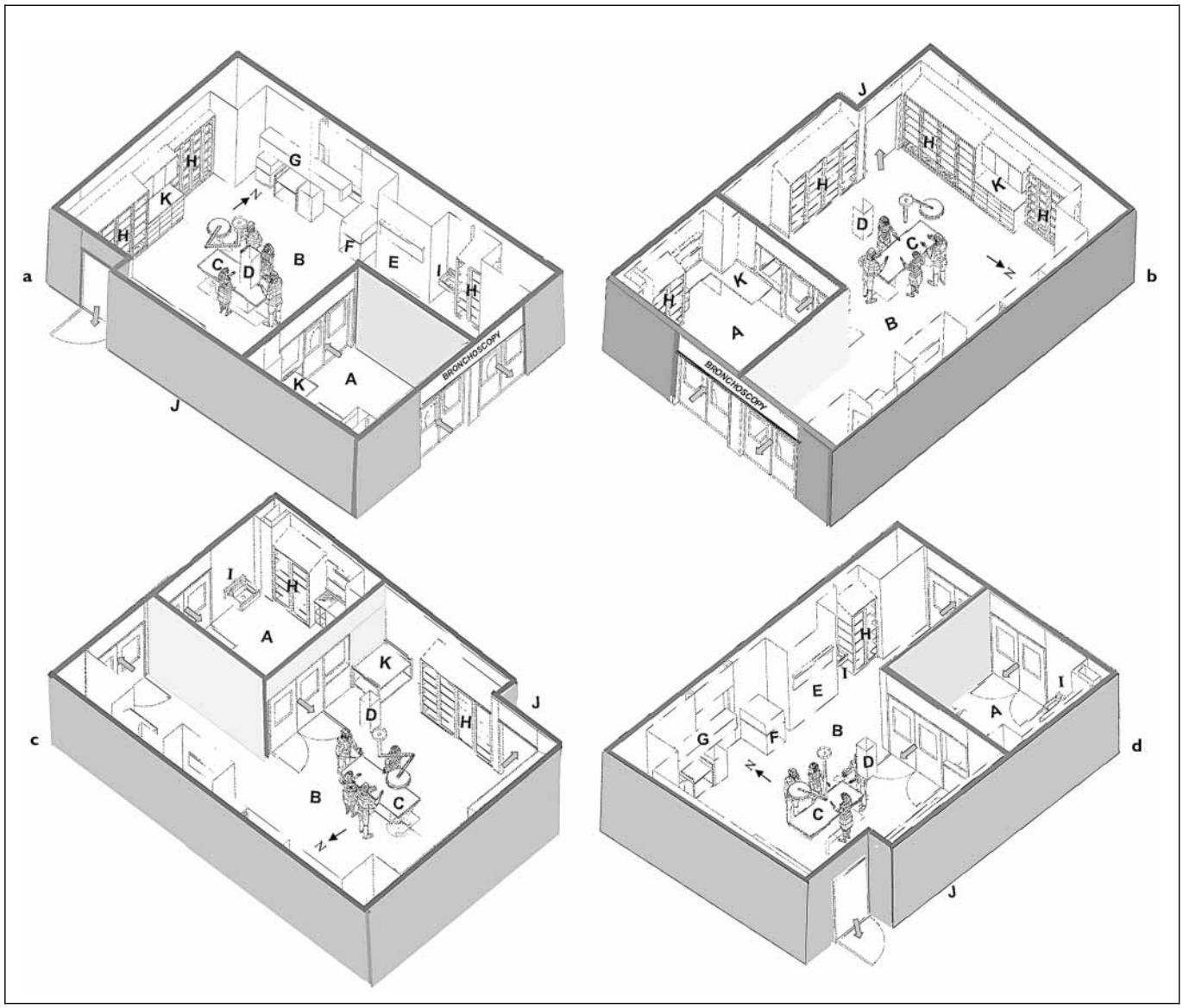

Fig. 1. The architect's drawing of the floor plan of the present bronchoscopy suite at Mayo Medical Center, Rochester, Minn., USA, seen from above, and from four different perspectives (**a–d**). The black arrow and the letter N provide orientation.

A = Preparation (and induction) room
B = Bronchoscopy suite
C = Surgical bed
D = Ceiling-mounted power source for bronchoscopy light sources and anesthetic gases
E = View box for imaging studies
F = Nd:YAG laser
G = Argon-dye laser
H = Storage spaces
I = Wash basin
J = Supply core and storage area
K = Paper work area

ogists is readily available [2]. Other interventional pulmonology procedures, such as thoracoscopy, transthoracic needle aspiration, percutaneous tracheostomy, endoscopic ultrasound-guided procedures will require special equipment and personnel. Irrespective of where the bronchoscopy is performed, personnel and equipment to provide resuscitation should be readily available.

An example of a fully equipped bronchoscopy room at the Mayo Medical Center, Rochester, Minn., is provided in figures 1–3. The room was designed by the bronchosco-

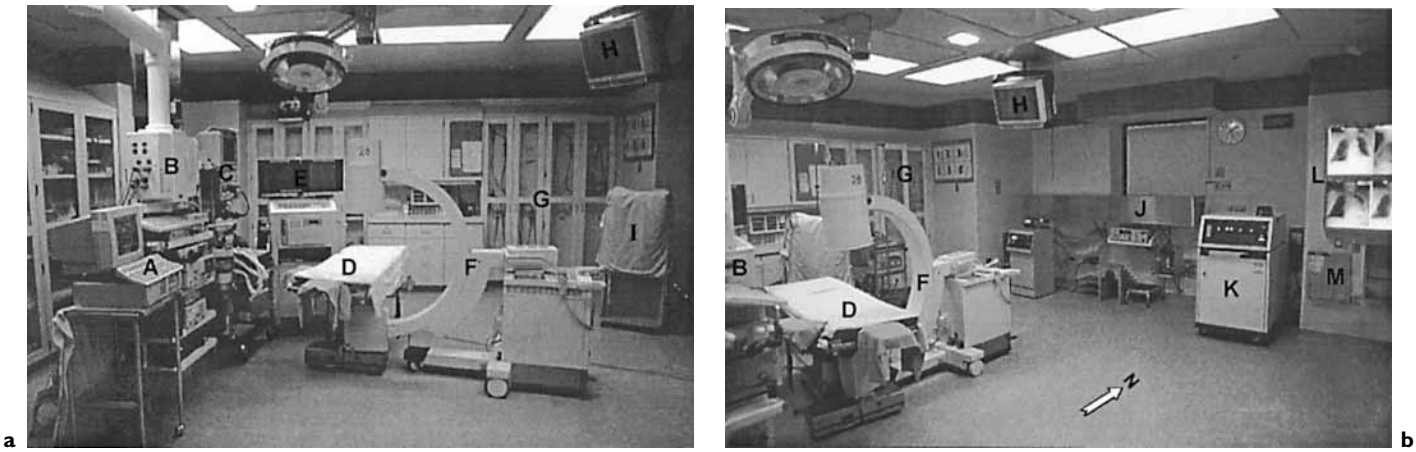

Fig. 2. Several views of the bronchoscopy suite depicted in figure 1 showing a view looking to the west (**a**) and to northwest (**b**).

A = Image management equipment
B = Ceiling-mounted mobile column with all light sources, camera heads and video system
C = Ceiling-mounted mobile anesthesia delivery system
D = Surgical bed
E = Mobile dual fluoroscopy monitor with biplane fluoroscopy capability
F = Mobile 'C-Arm' fluoroscopy unit
H = Ceiling-mounted video monitor to visualize bronchoscopy procedures
I = Lead-coated aprons to shield from radiation
J = Argon-dye laser
K = Nd:YAG laser
L = View box for imaging studies
M = Storage area or medical records and imaging studies

The room is also equipped for surgical procedures. The letter N and the arrow provide orientation.

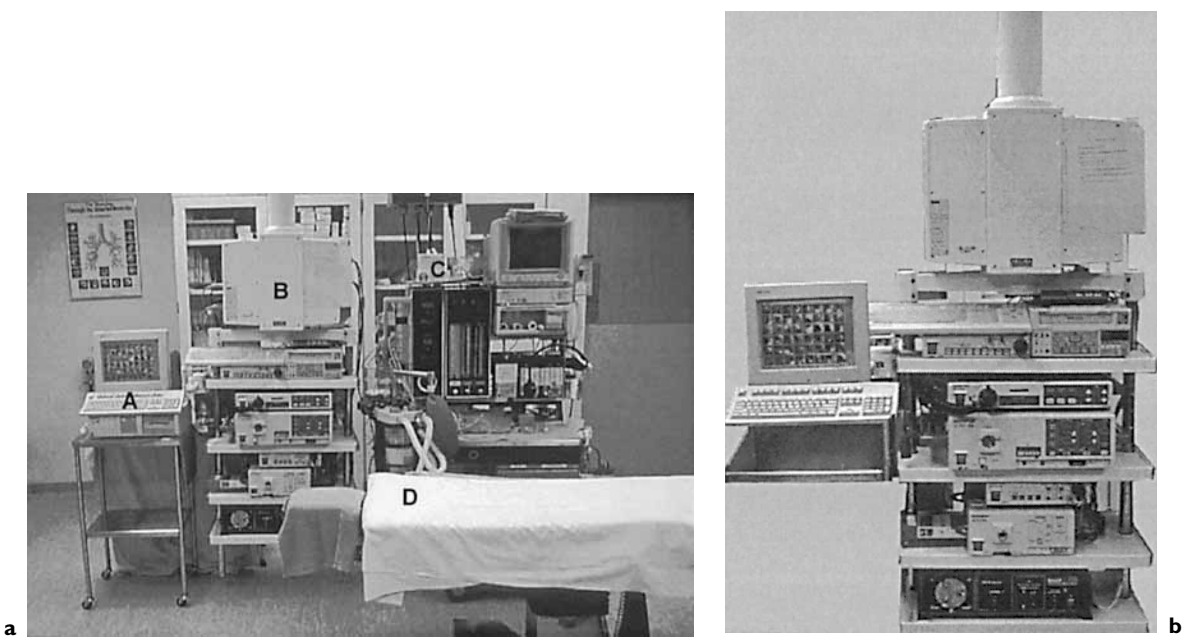

Fig. 3. a Convenient arrangement of imaging equipment (A), ceiling-mounted mobile column for bronchoscopy light sources (B), column-mounted mobile system for anesthesia delivery (C), and a surgical bed (D). **b** Close-up view of ceiling-mounted mobile column with power supply and columnar arrangement of various light sources for flexible and rigid bronchoscopy, video recording and playback system, and keyboard system for data entry.

pists and nonphysician bronchoscopy personnel and architects. The dedicated suite is equipped for general anesthesia and all types of bronchoscopic procedures in adults and children. Such a dedicated unit next to other operating rooms provides the bronchoscopists with an opportunity to offer optimal services to patient. Clearly, such an exclusive unit is neither necessary nor realistic in all medical centers. However, a busy bronchoscopy practice will benefit from a dedicated unit that is fully equipped for all types of bronchoscopy procedures. Ultimately, several factors contribute to the choice of location for the procedure and choice of assistants such as personal preference, convenience, available facilities and availability of personnel or paramedical training programs [1]. Financial considerations play the determining role in these decisions.

Patient Preparation Area

This area should be adjacent to the procedure area and is primarily designed for administration of premedications and instillation of topical anesthesia prior to bronchoscopy. A distinct patient area is not an absolute requirement. However, a separate preparation locale is timesaving in a busy bronchoscopy practice when one patient can be prepared in this area by assistants as the bronchoscopist completes an earlier case. The bronchoscopist and the bronchoscopy team should assemble the minimum equipment required to prepare the patient. Easy accessibility of supplemental oxygen and resuscitation equipment is imperative. The bronchoscopist should be able to prepare the patient single-handedly unless the patient is too sick to adequately cooperate and requires additional help from a nurse, surgical technician or another physician.

The Procedure Area

The procedure area should remain uncluttered so that the bronchoscopist and the assisting personnel can move around the patient's head area and be able to perform various bronchoscopic maneuvers and manage unforeseen complications. The patient can be in the seated or supine position on an operating table, in a patient bed, a chair or in a chair similar to the one used by dentists. Irrespective of the type of table or chair used, the bronchoscopist should be able to place the patient in the reverse Trendelenburg position in case of severe bronchoscopy-induced bleeding or hypotension. The instruments used should be easily accessible to the bronchoscopist and the main assistant. If general anesthesia is required, appropriate equipment should be available. Adequate space should be available to bring in special equipment such as a fluoroscope and laser unit.

The Postbronchoscopy Area

This area is primarily for observation of the patient after bronchoscopy is completed. Since almost all patients require a period of observation to ensure that there are no complications from the pharmaceutical agents used during the procedure or the procedure itself, a designated area for observation is necessary. Depending on the setup at each medical center, this area may include the bronchoscopy unit itself, a postsurgical recovery unit, a room adjacent to the bronchoscopy unit, a waiting room or the patient's room itself if bedside bronchoscopy is performed.

In the survey of North American bronchoscopists, 56% reported that they used an area adjacent to the bronchoscopy unit as the postbronchoscopy recovery area, whereas 43% used a separate area such as an outpatient waiting area, the procedure room itself or the emergency room for this purpose [7]. In the AAB survey mentioned above, only 28% of the 744 North American bronchologists indicated that they had a dedicated unit for bronchoscopy which was also used as the postbronchoscopy recovery area [8]. Postbronchoscopy observation should be undertaken by the bronchoscopist, another physician or a nurse trained to recognize postbronchoscopy complications.

The Bronchoscopy Equipment

The types of bronchoscopes required depend on the needs and the type of bronchoscopy practice. The minimum requirements to perform flexible bronchoscopy to obtain biopsies of the lesions in the tracheobronchial tree and therapeutic bronchoscopy in adults include an adult-size flexible bronchoscope, a light source, several cytology brushes and biopsy forceps, specimen containers, suction apparatus, and supplemental oxygen and equipment for resuscitation (fig. 4). Premedications, sedatives, and topical anesthetic agents are also necessary for most procedures. Even in the absence of a large-volume bronchoscopy practice, the bronchoscopist is well advised to have an extra bronchoscope and several biopsy forceps in case of breakdown of the equipment [2]. All other types of bronchoscopic procedures such as rigid bronchoscopy, laser bronchoscopy, brachytherapy, cryotherapy and stent placement will require additional instruments (fig. 5). Likewise, pediatric bronchoscopy will require an entirely separate set of instruments and accessories [10, 11].

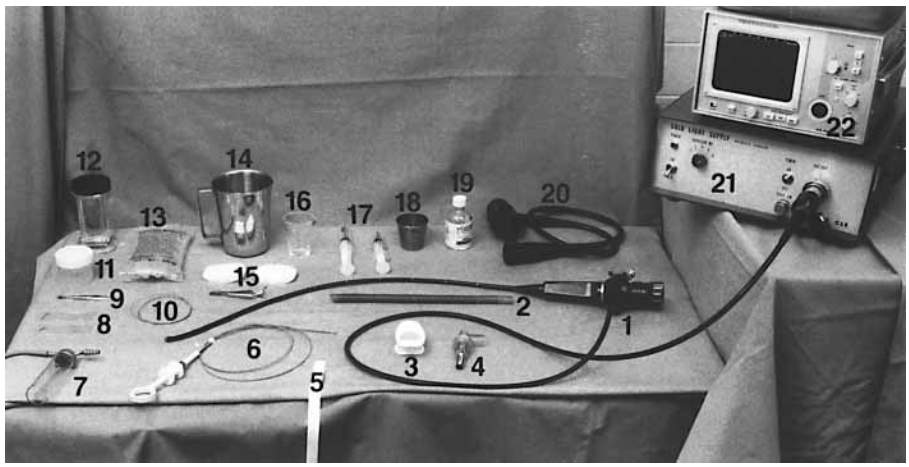

Fig. 4. Minimal requirements for performing flexible bronchoscopy.

1 = Flexible bronchoscope
2 = Soft, uncuffed and noncollapsible endotracheal (ET) tube
3 = Bite-block (mouthpiece)
4 = ET tube adapter for supplemental oxygen delivery
5 = 20-cm-long adhesive tape to fasten ET tube
6 = Flexible biopsy forceps
7 = Sterile glass container to collect bronchial lavage
8 = Glass slides for cytologic smears
9 = Pick-up forceps to remove biopsy specimens from biopsy forceps
10 = Bronchial brush
11 = Specimen jar with formaldehyde
12 = Slide container with 95% alcohol
13 = Lactated Ringer's solution for bronchial lavage
14 = Metal container with warm water to defog and clean the bronchoscope tip
15 = Eye pads and towel clip
16 = Medicine jar with lactated Ringer's solution
17 = Syringes – one with lactated Ringer's solution and the other containing 4% lidocaine
18 = Metal cup containing 4% lidocaine
19 = 4% lidocaine
20 = Lecture scope
21 = Cold-light source
22 = Electrocardiographic monitor

Not shown in the figure are a tube of lubricating jelly and gauze pads. Figure reproduced from *Seminars in Respiratory Medicine* [43].

The Bronchoscopes

The bronchoscopes, both flexible and rigid, are manufactured by various manufacturers. The bronchoscopist should acquire the appropriate equipment based on what the practice requires. The number and types of the bronchoscopes required will depend on the needs of each individual bronchoscopist. The bare minimum required is described above. While comparison of various types of bronchoscopes by different manufacturers is beyond the scope of this writing, certain general recommendations can be provided. The reliability of the manufacturer for prompt delivery of service, accessories, repairs and replacement of damaged equipment is very important. The bronchoscopists should be cognizant of the fact that instruments made by one manufacturer may not be compatible with those made by a different manufacturer. Therefore, it is better to purchase the bronchoscope and related equipment made by the same manufacturer.

A bronchoscopist involved in all aspects of bronchoscopy may require flexible and rigid bronchoscopes of various sizes to accommodate adults as well as pediatric patients. Several types of both flexible and rigid bronchoscopes will be required if laser bronchoscopy, stent placement and removal of foreign bodies are to be undertaken. Pediatric bronchoscopy will require ultrathin flexible bronchoscopes and rigid bronchoscopes of smaller diameters.

Cytology Brushes for the Flexible Bronchoscope

Both disposable and reusable brushes are available for obtaining cytological specimens from airways and pulmonary parenchymal lesions. Brushes are sheathed or unsheathed and lined with bristles that have varying degrees of stiffness or flexibility. Models with varying bristle sizes are also available. The efficacies of various cytology brushes have been studied. One study examined the cellular yield expressed as the number of cells recovered with two different types of sheathed cytology brushes, one with slightly longer and wider bristles. The latter provided greater yield in total number of cells recovered per brush [12]. On the other hand, another study used sheathed brushes of 1.00, 1.73 and 3.0 mm diameter and showed

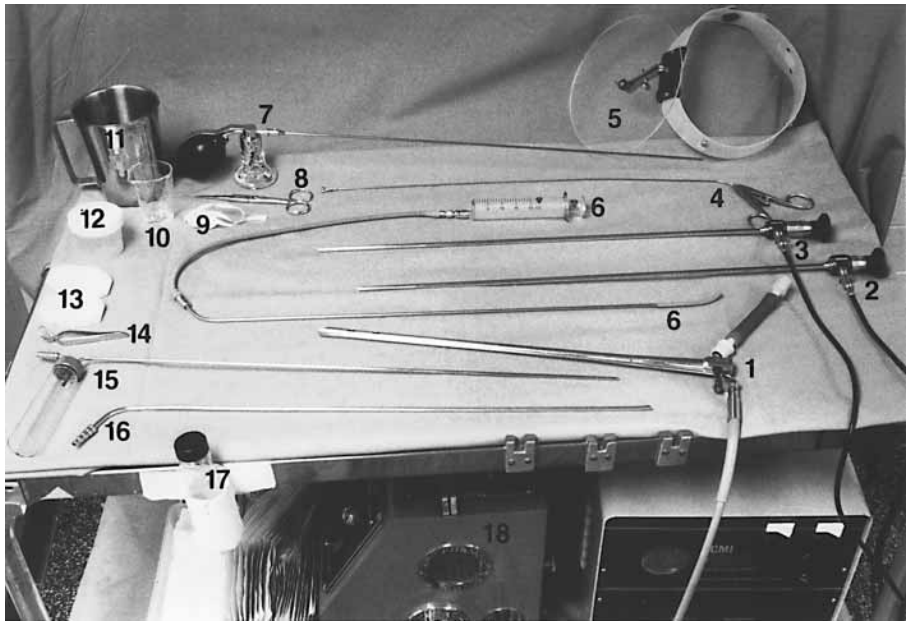

Fig. 5. Minimal requirements for performing rigid bronchoscopy.

1 = Rigid bronchoscope with light supply cord below and oxygen delivery tube above
2 = Straight-view telescope
3 = 90° view telescope
4 = Biopsy forceps
5 = Eye shield
6 = Syringe and long rubber-tipped metal tube for bronchial lavage through rigid bronchoscope
7 = Atomizer containing 4% lidocaine – for topical anesthetic application through rigid bronchoscope to anesthetize bronchial mucosa
8 = Pair of scissors
9 = 'Umbilical tape' to pack severely hemorrhaging bronchus
10 = Medicine cup containing lavage fluid
11 = Container with warm water to clean biopsy forceps, telescope tips etc.
12 = Specimen jar with formaldehyde
13 = Eye pads
14 = Towel clip
15 = Container to collect bronchial lavage fluid
16 = Long suction cannula
17 = Bronchial lavage container
18 = Light source

Figure reproduced from *Seminars in Respiratory Medicine* [43].

no significant difference in cell recovery among the three brushes [13]. It is important to recognize that the technique of brushing and preparation of cytology smears is far more significant than the type of brushes used [14].

Biopsy Forceps for the Flexible Bronchoscope

The standard adult flexible bronchoscopes have working channels that range from 2.0 to 2.8 mm in diameter. Biopsy forceps that can traverse this channel come in several sizes and shapes. There are no specially designed forceps that can traverse the working channel of pediatric (ultrathin) flexible bronchoscopes. The three basic types include those with serrated edge (alligator), smooth edge with fenestrated or unfenestrated cups and 'spiked' (impaler needle between the cups). Some forceps are manufactured with longer blades. The latter type of forceps is helpful in obtaining a biopsy from mucosal abnormalities along the tracheal wall or from lesions from which the regular forceps easily slip or slide. All forceps have a proximal control part and the forceps itself at the distal tip.

The choice of biopsy forceps depends on the individual bronchoscopist and the performance of the forceps. Wang et al. [15] studied the efficacy of three different types of forceps to obtain bronchoscopic lung biopsy and reported that larger forceps and serrated forceps provided larger specimens, but the size of the biopsy specimen itself did not significantly alter the diagnosis. The nondisposable forceps have finite life, and a study observed that biopsy forceps become dull after 20 or 25 applications [16].

Biopsy Forceps for the Rigid Bronchoscope

Many types of forceps are available for use with the rigid bronchoscope. The numerous types of forceps permit handling almost all types of problems within the airways. Bronchoscopic lung biopsy can be obtained with special forceps via a rigid bronchoscope [17]. Specialized

forceps are available for removal of various types of foreign bodies. In design, the forceps are usually much larger than those used with the flexible bronchoscope, slightly rigid in performance and stronger. The forceps for use with the pediatric rigid bronchoscope are identical in structural details but smaller in size.

Bronchoscopy Needles

Bronchoscopic needle aspiration and biopsy are commonly used in the staging of lung cancers. They are frequently employed to sample paratracheal, hilar and subcarinal lymph nodes. Almost all needles available on the market are disposable. Two sizes (19 and 21 gauge) are available; the larger needle is used to obtain tissue biopsy, whereas the smaller needle is designed for obtaining cytology aspiration. Retractable and nonretractable needles as well as metallic and plastic needles are available. Many manufacturers have discontinued the sale of nonretractable needles because of the high risk of injury to the inner lining of the flexible bronchoscope.

Baskets and Claws

These are used to extract aspirated tracheobronchial foreign bodies, thick mucous plugs and clots. These accessories are rather flimsy and not as effective as instruments available for removal of foreign body with a rigid bronchoscope.

Protected Catheters

The protected catheter brushes are used for obtaining respiratory specimens for bacterial culture [18–20]. Various types are available and all are meant for single use. The preference for these catheters depends on individual bronchoscopist and the performance of the catheter. In recent years, bronchoalveolar lavage has almost totally replaced the protected specimen brush for obtaining specimens for bacterial cultures.

Specimen Traps

Several types of specimen traps are available to collect bronchial washings and bronchoalveolar lavage effluent. Special containers to hold cytology slides and biopsy specimens are commercially available. Many bronchoscopists improvise their own system with spare parts. Major medical centers may have these manufactured to their specifications. The bronchoscopist is well advised to discuss her/his needs with the personnel in the pathology and microbiology laboratories so that a mutually acceptable equipment is designed and procured.

Fluoroscopy

The fluoroscopes used as adjuncts to bronchoscopy machines are either fixed or mobile (portable). If the mobile unit is not available, the patient will have to be transported to the location of fluoroscopy unit, generally in the chest roentgenology unit. The mobile units are greatly helpful in obtaining bronchoscopic lung biopsy in patient rooms and other areas (fig. 2). The fluoroscopy units are expensive and therefore, a fluoroscopy unit dedicated only to bronchoscopy is not realistic for most bronchoscopists. The mail survey of 871 bronchoscopists in North America noted that fluoroscopy facility dedicated to bronchoscopy was reported by 20.9% of the respondents and fluoroscopy was shared with nonbronchoscopists by 74.1%.

Fluoroscopic guidance assists in reaching localized lesions in the lung parenchyma. It also helps reduce the incidence of pneumothorax following bronchoscopic lung biopsy. The safety of outpatient bronchoscopy, including bronchoscopic lung biopsy, is well documented [21–24]. Even though bronchoscopic lung biopsy can be performed without fluoroscopic guidance, the incidence of pneumothorax associated following bronchoscopic lung biopsy is less than 1.8% when fluoroscopy is used and the incidence significantly increases to 2.9% without fluoroscopy [25]. Another use for the fluoroscope is in the placement of airway stents.

Endotracheal Tubes

Endotracheal tubes to facilitate easy insertion of the flexible bronchoscope into the airways are not used by all bronchoscopists. However, many insert endotracheal tubes routinely prior to flexible bronchoscopy. To permit easy passage of most adult flexible bronchoscopes, the minimum inner diameter of the endotracheal tube required is 7.5 mm. While any type of endotracheal tube can be used, soft latex wire-spiral tubes, without cuff, are easier to use over a flexible bronchoscope and better tolerated by patients [26]. As the ultrathin flexible bronchoscopes used in pediatric practice have varying diameters (1.8–3.2 mm), endotracheal tubes of different diameters should be available if endotracheal intubation is planned.

The Monitoring Equipment

Noninvasive monitoring equipment such as sphygmomanometry, electrocardiographic monitoring and pulse oximetry are routinely used by most bronchoscopists. Pulse oximetry is useful to assess adequacy of oxygenation whether or not supplemental oxygen is given [27–29]. In

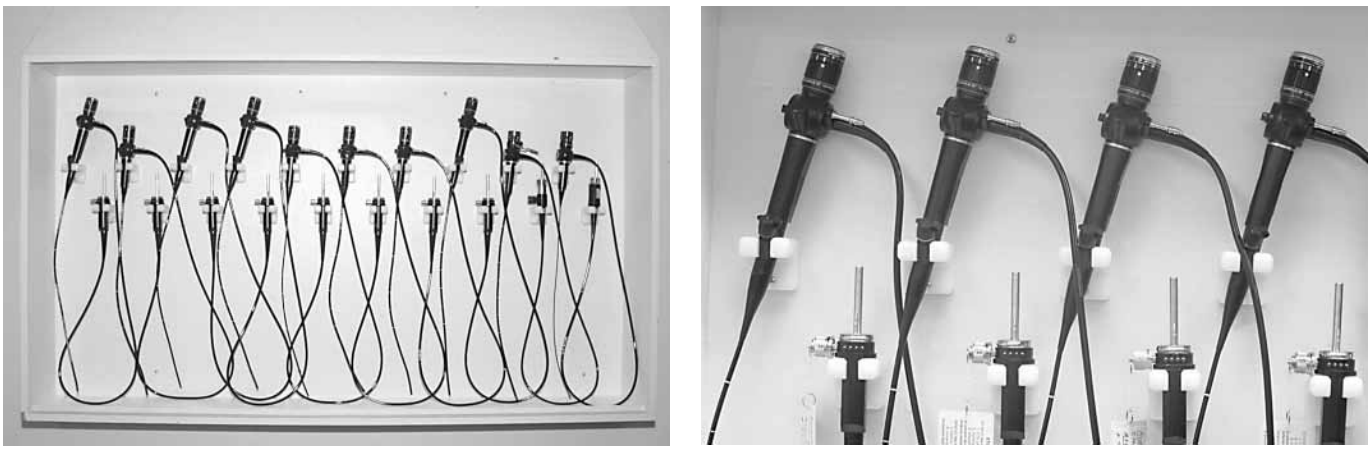

Fig. 6. Special storage cupboard for flexible bronchoscopes (**a**), and a close-up view (**b**). Hanging them as shown prevents development of curves in the shaft of the instrument. Figure reproduced with permission from Prakash et al. [2].

the ACCP mail survey [7], routine use of pulse or other oximetry was practiced by 84.2% of the respondents and electrocardiographic monitoring by 74.6%. Supplemental oxygen should always be available.

Other Equipment

Special equipment required for laser bronchoscopy, electrocautery, cryotherapy, airway stent placement, brachytherapy, airway dilatation, phototherapy, bronchoscopic ultrasound and other emerging technologies are discussed elsewhere in this book.

Suction apparatus, extra tubings, cleaning materials and commonly used pharmaceutical agents are among the miscellaneous equipment necessary for the optimal practice of bronchoscopy. All equipment and medications necessary for cardiopulmonary resuscitation should be readily available at bronchoscopy location.

The Storage Area

The size of the storage for the bronchoscopy equipment area depends on the diversity of bronchoscopy practice. If a bronchoscopist limits her/himself to simple bronchoscopy (only flexible bronchoscopy and no pediatric bronchoscopy or other special procedures), then all the bronchoscopy equipment can be stored in a mobile cart in a corner of a storage room in the hospital or office. Bronchoscopists specializing in laser bronchoscopy, rigid bronchoscopy and other complex procedures will require more spacious areas to store their equipment [2]. The flexible bronchoscope is a delicate instrument and requires proper handling and storage (fig. 6).

Expertise

Bronchoscopy should be performed by physicians who are skilled and appropriately trained in the procedure. It is unclear how many procedures one should perform under tutelage to achieve proficiency in routine bronchoscopy. The eligibility requirements to obtain certification in pulmonary diseases by the American Board of Internal Medicine do not specify the performance of a minimum number of bronchoscopies during the training [30]. The American Board of Thoracic Surgery requires its candidates to have performed at least '25 bronchoscopy and esophagoscopy' procedures [31]. An individual who completed training in pulmonary diseases oberved that at least 100 bronchoscopies were needed to become proficient [32]. Others have indicated that to become proficient in bronchoscopy, performance of 50 to 100 bronchoscopies is necessary [33]. Some physicians, in spite of 'performing' many more than 50 bronchoscopies, may remain inept and lack confidence in achieving proficiency in the procedure. Therefore, the decision whether someone is competent to perform bronchoscopy should not be based on the basis of the number of bronchoscopies performed. The program director or the director of bronchoscopy at the training institution should judge and certify the competence of each candidate and recommend and provide remedial training if necessary [7]. It is also important that the training of the bronchoscopists should include assisting the bronchoscopist during bronchoscopy and related procedures.

A national mail survey of 736 members of the American College of Physicians who were identified as practicing pulmonologists in the USA observed that flexible bronchoscopy was performed by 96% pulmonologists, bronchoscopic needle aspiration by 77%, foreign body removal by 83%, rigid bronchoscopy for biopsy or removal of foreign body by 8% and Nd:Yag laser therapy by 13% [34]. When asked about (1) number of procedures they did in the previous year, (2) number of procedures per year needed to attain proficiency and (3) number of procedures per year required to maintain proficiency, the respondents answered (median numbers shown for the three variables) in the following way: flexible bronchoscopy 100, 50 and 24, bronchoscopic lung biopsy 25, 20 and 10, and laser phototherapy 5, 10 and 5. Among these pulmonologists, bronchoscopy training was obtained through formal training by 53%, through attending course/s by 7% and on their own by 42% of the respondents [34]. An editorial urged the major pulmonary and critical care societies to enact comprehensive guidelines for granting hospital privileges to perform the major procedures. It also recommended well-designed 'mini-fellowships' of 2–16 weeks duration for introducing physicians in clinical practice to major new procedures that were not taught during formal fellowship training [35]. This will be difficult to accomplish because of the problems associated with organizing 'on hands' training for large groups of physicians. Short didactic courses (without actual practice) may not provide sufficient supervised training to attain proficiency. Strict guidelines will undoubtedly generate disagreements among clinicians. Nevertheless, well-defined guidelines are likely to prevent improper and conceivably superfluous (as well as life-threatening) procedures [36].

At least 50 bronchoscopy procedures may be necessary to become competent in routine flexible bronchoscopy [7]. This should include biopsy of visible tracheobronchial lesions, bronchoalveolar lavage and therapeutic bronchoscopy. At least 50 bronchoscopies per year may be necessary to remain competent in the procedure. One study that assessed the extent of training required to attain competency in bronchoscopic needle aspiration observed that to achieve acceptable results from this procedure, a training period that includes about 50 procedures is required [37]. Another study over a 3-year period during which serial multifaceted educational interventions directed toward bronchoscopists and their technical staff were provided observed that diagnostic yield from bronchoscopic needle aspiration increased significantly from 21 to 48% [38].

In the ACCP survey, when asked about the number of bronchoscopies required to become and remain competent in the procedure, more than 60% of respondents recorded that at least 50 procedures were necessary to become competent. More than half the survey participants noted that at least 25 bronchoscopies per year were required to remain competent [1]. In the more recent survey conducted by the AAB, when asked about bronchoscopy training during their fellowship, the responses were as follows: training in flexible bronchoscopy (95%), rigid bronchoscopy (27%), laser procedures (24%), stent insertions (23%), brachytherapy (31%), cryotherapy (22%) and bronchoscopic electrocautery (22%). Many had received training 'on the job', particularly in brachytherapy, rigid bronchoscopy, laser procedures, stent insertion, cryotherapy and electrocautery. Another source of training was through the 2-day courses in interventional broncholology[8].

The ACCP survey indicated that bronchoscopists are divided on whether or not rigid guidelines for bronchoscopy should be established [1]. In the AAB survey, only 2% of the respondents felt they needed additional instruction or education in flexible bronchoscopy, but many more expressed a need for additional information on stent insertion (59%), laser procedures (43%), cryotherapy (39%), electrocautery (37%) and brachytherapy (31%). Over one-fifth of the respondents felt no need for additional instruction or education in any of the procedures [8].

These surveys reveal that over the previous decade, about a quarter of the surveyed physicians had received training in therapeutic bronchoscopic procedures during their felloships, compared to only 8% of bronchoscopists surveyed in 1989. When asked whether the AAB, ACCP and American Thoracic Society should provide detailed guidelines pertaining to the practice of flexible bronchoscopy, 87% answered affirmatively and 11% negatively. A significant number of respondents (71%) mentioned that laser procedures and stenting should be performed only in tertiary care facilities, and 51% of the respondents felt that interventional techniques should be taught during part of a routine pulmonary fellowship. The two major procedures respondents believed should be taught were brachytherapy (52%) and stent insertion (51%) [8]. These responses indicate that many bronchologists feel the need for practice guidelines and specialized training in certain procedures. It is obvious that some novices attain proficiency sooner than others do, and some may never feel 'comfortable' enough to perform certain complicated procedures. Maintenance of competence is more dependent on performance of the procedure on a regular basis rather than the numbers alone.

The Bronchoscopy Personnel

The mail survey described above reported that nurses alone assisted 39% of the bronchoscopists during the procedure whereas 26% of the bronchoscopists employed nurses and other assistants; respiratory therapists were the sole assistants to 14.7% of the bronchoscopists, and 7.6% of physicians were assisted by respiratory therapists and others (nurses, laboratory technicians, residents). Pulmonary function technicians and other paramedical personnel assisted 12% of the bronchoscopists. Physicians were mentioned as bronchoscopy assistants by 15% [7]. Since many bronchoscopy units are adjacent to or part of a pulmonary function testing laboratory or respiratory therapy department, many train the technicians in these areas to assist in bronchoscopy. As in any surgical procedure, the team concept is vital to the performance of bronchoscopy.

Training of Paramedical Personnel

Many routine flexible bronchoscopy procedures can be carried out by a well-trained bronchoscopist without others to help during the procedure. However, most complicated procedures and a busy bronchoscopy practice warrant additional assistance. Ideally, 2 trained persons, other than the bronchoscopist, will help in achieving optimal bronchoscopy practice. The assistants can be physicians, nurses, surgical technicians or other paramedical personnel trained in bronchoscopy assistance and maintenance of the equipment. Paramedical personnel who wish to assist during bronchoscopy procedures should be provided education and instructions in the basics of bronchoscopy and related procedures. This can include a period of observation of the procedure and assisting the already trained bronchoscopy nurse/surgical technician. Initially, the trainee should be taught the basic anatomy of the tracheobronchial tree, the reasoning behind the procedures, a working knowledge of the equipment, indications and contraindications, potential complications, paper work related to the procedures, and administrative policies and procedural details pertaining to the institution.

Next, the trainee should be encouraged to observe all aspects of bronchoscopy and related procedures, beginning with the preparation of the patient and ending with the care of the patient after bronchoscopy and final dismissal. The period of observation and training should also include maintenance and cleaning of the bronchoscopy equipment.

The third phase of the training consists of active participation of the trainee in assisting the bronchoscopy nurse/technician. The responsibilities are gradually increased, and the trainee is able to comfortably assist the charge nurse/technician in complex procedures. During this period, the bronchoscopist and the charge nurse/technician should correct any deficiencies and provide remedial training if necessary.

The final phase consists of the fully trained nurse/technician being in charge of the organization of the bronchoscopy procedures and in ascertaining that each procedure is smoothly organized and completed. Periodic didactic sessions in continuing education in the procedure and new developments should be encouraged to maintain competence.

As observed above in the discussion of training of bronchoscopists, the personnel assisting the bronchoscopist in specialized procedures such as laser, brachytherapy, stenting and other procedures should be familiar with the equipment and instructed in its care and maintenance.

The Anesthesiologist and the Nurse Anesthetist

Routine assistance from the anesthesiologist or the nurse anesthetist is seldom required for routine flexible bronchoscopy procedures in adults because almost all of these procedures can be performed without general anesthesia. Nearly 8% of the participants in the mail survey routinely used assistance from the anesthesiologist/anesthetist during bronchoscopy and 16.5% used general anesthesia for bronchoscopy [7]. A mail survey of the British bronchoscopists reported that general anesthesia was used by 12% [25]. Technically difficult procedures, most rigid bronchoscopies, most time-consuming laser bronchoscopies and extreme patient apprehension are situations where general anesthesia may be required. Pediatric rigid bronchoscopy in children warrants general anesthesia. Currently, most bronchoscopists use intravenous sedation for flexible bronchoscopy. A nurse or a physician to assist with intravenous access and to administer sedation as needed is highly desirable.

Mobile or Portable Bronchoscopy Unit

Dedicated bronchoscopy units or operating rooms are not necessary to perform all types of bronchoscopy procedures. Indeed, 55% of the bronchoscopists in the North American survey reported that they employed bronchoscopy at the bedside in the patient's room [7]. The bronchoscopists who prefer to provide the bronchoscopy service in the patient's room should develop and maintain a

Fig. 7. The mobile bronchoscopy unit equipped to help the bronchoscopist perform most of the commonly required flexible bronchoscopic procedures. This unit can be easily taken to the intensive care unit or to the patient's room for bedside bronchoscopy. Figure reproduced with permission from Prakash et al. [2].

Table 1. Equipment required for bronchoscopy in the critical care unit[1]

Flexible bronchoscope
Light source for the bronchoscope
Topical anesthetic
Sedatives for intravenous administration
Endotracheal tube (>7.5 mm OD)[2]
Sphygmomanometer
Electrocardiographic monitor
Pulse oximetry
Supplemental oxygen
Suction apparatus
Specimen trap
Sterile saline
Iced sterile saline
Epinephrine (1:1,000)
Biopsy forceps (for removal of mucous plugs and blood clots)
Syringes, gauze, lubricant, plastic tubing

Table modified from Prakash [39]. OD = Outer diameter.
[1] Minimal requirements are listed.
[2] Bronchoscopes with larger OD (>6.0 mm) may require an endotracheal tube with an OD >8.0 mm.

mobile bronchoscopy unit to facilitate the optimal performance of the procedure. The major disadvantages and advantages of doing bronchoscopy in patient's room are discussed above. In our practice, although a fully equipped bronchoscopy unit is available 24 h a day (fig. 1–3), my colleagues and I use a mobile cart to perform many flexible bronchoscopy procedures in the intensive care unit, non-bronchoscopy operating rooms and occasionally in non-intensive care patients' rooms (fig. 7). Such mobile bronchoscopy carts should be stocked with equipment necessary to carry out the most commonly performed flexible bronchoscopy procedures such as diagnostic bronchoalveolar lavage and therapeutic removal of secretion, mucous plug and blood clots. If bronchoscopic lung biopsy and endobronchial biopsies are planned, it is perhaps prudent to do these in special areas where facilities and personnel are available to handle complications.

Most critical care or intensive units in major medical centers are equipped with mobile bronchoscopy carts dedicated for use in the intensive care unit, and respiratory therapists are trained in the care and set up of the equipment. Minimum requirements to perform bronchoscopy in the critical care unit are listed in table 1 [39]. Patients admitted to the intensive or critical care unit may require transportation to another area for certain bronchoscopic procedures such as laser therapy and bronchoscopic lung biopsy.

Safety

The organization of a dedicated bronchoscopy unit and training of the bronchoscopy team also includes establishment of well-defined rules to ensure the safety of all personnel and patients. A precaution against spread of infections is an important component of this philosphy. Universal infection control precautions as well as proper maintenance of equipment will prevent the occurrence of true as well as pseudoinfections associated with bronchoscopic procedures [40, 41].

Bronchoscopists and assistants are subject to radiation exposure during bronchoscopy procedures such as bronchoscopic lung biopsy, bronchoscopic brushing or needling or peripheral lesions, brachytherapy, insertion of airway stents and fluoroscopy after lung biopsy to exclude

pneumothorax. The fluoroscopic equipment used for these procedures must be maintained in proper condition, and all personnel inside the bronchoscopy suite must be instructed to wear appropriate radiation shields. Radiation safety is part of bronchoscopy practice [42].

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General Aspects of Interventional Bronchoscopy

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Anesthesia for Interventional Bronchoscopy

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Summary

Perioperative anesthesiologic management of patients presenting for interventional bronchoscopy requires a multidisciplinary approach with optimal communication, adequate preoperative evaluation and preparation of patients, experience in alternative ventilatory techniques, availability of extended monitoring, and access to postoperative intensive care treatment including mechanical ventilation. Preoperative evaluation aims at identifying patients at risk for perioperative adverse events, especially regarding cardiovascular and pulmonary morbidity and optimizing ongoing therapies. Premedication strategies as well as guidelines concerning preoperative fasting and prevention of pulmonary aspiration are discussed. Interventional bronchoscopy is usually performed using topical local anesthesia for awake fiberoptic bronchoscopy and general anesthesia for rigid bronchoscopy. Ventilatory support can be provided by various modes, including spontaneous assisted ventilation using the laryngeal mask airway, endotracheal tubes or the rigid bronchoscope, intermittent positive pressure ventilation, and jet ventilation. During interventional bronchoscopy, short episodes of hypoxemia and hypercarbia are frequent problems which usually may be controlled with modification of the applied ventilation technique, whereas major hemorrhage and pneumothorax are more serious but fortunately rare complications.

Perioperative management of patients presenting for interventional bronchoscopy is a challenging task requiring a multidisciplinary approach with optimal communication between team members, distinct strategies for worst case scenarios and sufficient personnel resources (fig. 1). Rigid bronchoscopy has been superseded by flexible fiberoptic bronchoscopy for the assessment of airway, lung or thoracic disease, but is still a widely used technique for preoperative assessment before staging procedures and further thoracic interventions. Besides, rigid bronchoscopy is also preferred in pediatric bronchoscopy, massive hemoptysis, removal of foreign bodies, stent insertion, endosonography and endoscopic tumor resection. The application of this technique requires that the responsibility for the management of the airway is shared between the endoscopist and the anesthesiologist [1]. Anesthetic management has to account for some typical characteristics of the surgical procedures: (1) interventions within the airways which may compromise airway patency and require alternative airway management techniques; (2) utilization of laser devices associated with fire hazard; (3) prevalence of localized or generalized lung disease, presenting with the potential of limited pulmonary function and an increased risk of intra- and postoperative pulmonary complications, and (4) urgency of intervention and lack of time for thorough preoperative evaluation and preparation (dyspnea, imminent asphyxia).

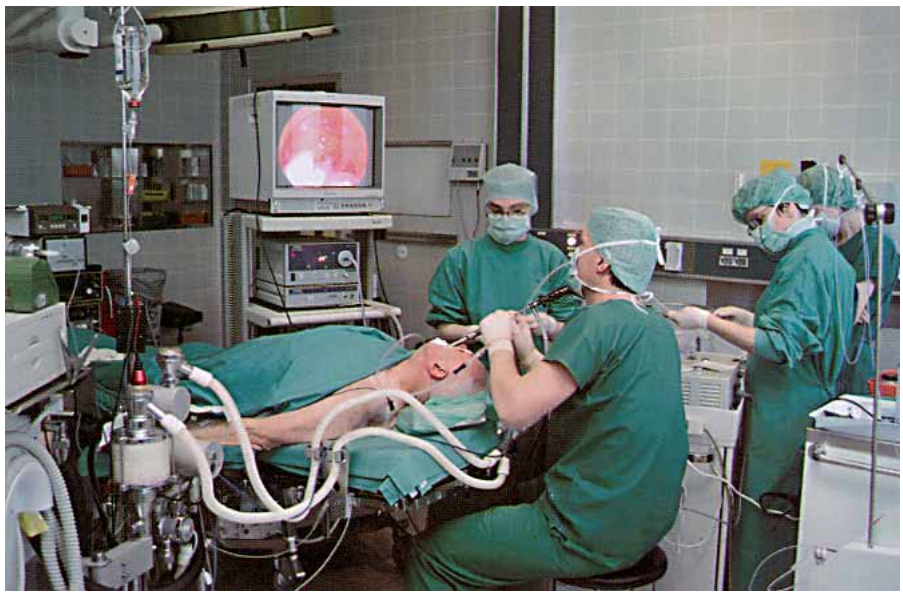

Fig. 1. Bronchoscopist performing video-assisted endobronchial laser surgery through the rigid bronchoscope. A fairly large theatre is necessary to accommodate equipment (laser device, video equipment, X-ray apparatus, anesthesia machine, jet ventilator, monitoring devices) and personnel (bronchoscopist, anesthetist, assisting nurses).

Therefore, successful performance of interventional airway endoscopy requires adequate preoperative evaluation and preparation of patients, experience in alternative ventilatory techniques, availability of extended monitoring devices and access to postoperative intensive care treatment including mechanical ventilation.

Preoperative Evaluation

The preoperative meeting of patient and anesthesiologist aims to satisfy the following requirements:

(1) Pertinent information about the medical history, current and previous medication, and physical and mental conditions of the patient. Patients should be asked to give details regarding untoward reactions to previous anesthetics, allergic reactions and familial disorders such as malignant hyperthermia and cholinesterase abnormalities. Records of previous surgical interventions should be consulted if available.

(2) Information of the patient concerning the planned anesthetic procedure and the postanesthetic strategy, instructions about the preoperative fasting period and the preoperative medications.

(3) Written informed consent on the anesthesiologic management which was previously discussed.

Preoperative evaluation allows to classify patients according to their physical status as suggested by the American Association of Anesthesiologists (table 1), and may give an estimate of the anesthesia-related morbidity and mortality. It aims at reducing perioperative morbidity by optimal preparation of patients for the surgical intervention, by helping to decide which anesthetic technique to be used, and by determining baseline organ functions, with which intra- and postoperative changes can be compared.

Table 1. The American Society of Anesthesiologists' (ASA) physical status classification

ASA I	A normal healthy patient
SA II	A patient with mild systemic disease
ASA III	A patient with a severe systemic disease that limits activity but is not incapacitating
ASA IV	A patient with an incapacitating systemic disease that is a constant threat to life
ASA V	A moribund patient not expected to survive 24 h with or without operation

Based on patient's history and physical status, measurements of hemoglobin, white blood cell count, platelet count, coagulation parameters, analysis of blood chemistry (sodium, potassium, creatinine, glucose, liver enzymes) and arterial blood gas analysis are performed. Procedures which may be complicated by considerable bleed-

ing may benefit from preoperative blood typing and search for irregular antibodies. A 12-lead electrocardiogramm (ECG) is performed in patients at risk for cardiac morbidity and in all patients with a clear indicative history. A chest radiograph may indicate areas of consolidation, bullae and signs of congestive heart failure. Pulmonary function tests (PFT) may be useful, but are no longer recommended as routine preoperative assessment of patients with respiratory disease [2]. However, pulmonary function and exercise tolerance may be considered to determine the postoperative strategy. Patients with an FVC below 15 ml/kg bodyweight, an FEV_1 below 1,000 ml and an FEV_1/FVC ratio below 35% of the predicted value as well as patients with preoperative hypercarbia are at increased risk for postoperative complications [3] and may benefit from monitored postoperative care for the first 24 h. Assessment of the reversibility of bronchial obstruction is important to guide perioperative therapy with inhaled β_2-receptor agonists and oral corticosteroids.

In patients with suspected or confirmed central airway obstruction, PFTs are essential before undergoing interventional bronchoscopy as the degree and sometimes the location of the obstruction can be detected by flow volume loops [4, 5].

Cardiac morbidity is increased in patients with a history of smoking, diabetes mellitus, arterial hypertension and hypercholesterolemia. The perioperative risk for coronary artery disease increases considerably with number and severity of recognized risk factors. Preoperative evaluation may detect patients at high risk for adverse intra- and postoperative cardiac events. Recently published guidelines for perioperative cardiovascular evaluation for noncardiac surgery [6] help to estimate the individual patient's cardiac risk using clinical markers (comprising major, intermediate and minor clinical predictors) and exercise tolerance or functional capacity in daily life. If a patient of advanced age having an abnormal ECG (as a minor clinical predictor) is able to climb a flight of stairs or walk up a hill without becoming short of breath, his probability of extensive coronary artery disease is small. Alternatively, if a patient becomes dyspneic and feels chest pain after minimal exercise, he may be considered at high risk for perioperative myocardial ischemia, tachyarrhythmias and especially right heart failure if concomitant pulmonary hypertension is severe. These patients benefit from extensive intra- and postoperative monitoring, aiming at preventing the adverse effects of hypercarbia and sympathoadrenergic stimulation due to the surgical procedure. Symptomatic patients or patients with a high cardiovascular risk may also benefit from optimizing an ongoing therapy (antihypertensive and antianginal medication, diuretics, ACE inhibitors), which aims at preoperative improvement of cardiovascular function.

Preoperative assessment of the airway anatomy is of considerable interest as patients may present with signs of hypoxemia or hypercarbia already at rest. Time for managing an unanticipated distorted airway anatomy may be dramatically shortened. Evaluation includes previous history of general anesthesias and physical examination of the interincisor distance, oropharyngeal classification according to the grading of Mallampati [7, 8], mandibular space length [9], motion range of the cervical spine, presence of beard, large breast and intraoral pathological states (infection, bleeding tumor).

Preoperative Fasting

The recommended preoperative fasting period has to differentiate between solid food and clear liquids. The traditional approach of 'nil after midnight' resulting in complete fasting periods of 8 h and longer has recently been questioned [10, 11]. There is no controversy that solid food should not be ingested for 8 h preoperatively to allow sufficient time for gastric emptying. Recent studies [12–14] evaluated the effects of preoperative drinking of clear liquids on gastric residual fluid amount and pH. As no difference compared with traditional overnight fasting was evident, it seems to be safe to permit liquid ingestion up to 2 h preoperatively [11, 15] in healthy, compliant patients scheduled for elective surgery and in the absence of known risk factors for aspiration.

Patients traditionally considered to be at risk for perioperative pulmonary aspiration include emergency patients (gastric contents of increased volume and/or acidity), obese and obstetric patients (increased intragastric pressure and decreased tone of the lower esophageal sphincter), patients with delayed gastric emptying (diabetics, patients on narcotics use, emergency patients) or patients with hiatal hernia or gastroesophageal reflux. They are treated prophylactically with H_2-receptor antagonists (ranitidine, cimetidine, famotidine) or proton pump inhibitors (omeprazole) and gastrokinetics (metoclopramide) [15].

Table 2. Premedication for interventional bronchoscopy (adults)

Sedatives[1]	
Midazolam	(7.5 mg p.o.)
Diazepam	(5–10 mg p.o.)
Lorazepam	(1–2 mg p.o.)
Temazepam	(15–30 mg p.o.)
Antisialagogues	
Atropine	(0.5 mg i.m., 1.0 mg p.o.)
Glycopyrrolate	(0.1–0.3 mg i.m.)
Scopolamine	(0.3 mg i.m.)

[1] Reduce dose in elderly or debilitated patients, and in patients at considerable risk of hypoxemia or hypercarbia.

Table 3. Monitoring during interventional bronchoscopy

Pulse oxymetry
Electrocardiography, ST-segment analysis
Blood pressure, noninvasive intermittent or continuously intra-arterial
Capnography
Nerve stimulator (neuromuscular monitoring)
Transcutaneous PCO_2 and PO_2

Premedication

Regular cardiovascular medication (especially antihypertensive drugs) and respiratory medication should be continued until the day of intervention. Patients on oral antidiabetics should omit these for the day of the procedure, accompanied by pre- and postinterventional control of the serum glucose levels. Patients on insulin medication receive a combination of intravenous glucose/insulin, together with frequent controls of the serum glucose level in order to prevent accidental hypoglycemia.

Specific procedure-related premedication (table 2) aims primarily at reducing anxiety and perioperative distress and secondarily at drying the airway. This medication has to be adapted to the individual needs of the patient as well as to the surgical procedure. Routine anxiolytic or amnestic premedication for bronchoscopic biopsy or bronchoalveolar lavage may not be necessary [16, 17], although some improvement in patient perception of the bronchoscopic procedure has been demonstrated using oral lorazepam which may be of advantage when a second bronchoscopy becomes necessary [18]. Antisialagogues like atropine, glycopyrrolate and scopolamine may have favorable effects on the duration and efficacy of topical airway anesthesia. If given 60–90 min before the procedure, the contact of the topical local anesthetic with the mucosa will be less impaired by secretions [19]. Glycopyrrolate is as effective in preventing respiratory tract secretion as atropine [20]. The pronounced sedative effect of scopolamine limits its use in patients at risk for hypoxemia. Prevention of parasympathetically mediated bradycardia and hypotension during the procedure is not sufficiently achieved with anticholinergic drug doses given to achieve dry airways. Intravenous supplemental doses (e.g. atropine 0.5 mg, glycopyrrolate 0.1 mg in adults) given immediately prior to the intervention are therefore needed to block vagal effects completely. More invasive procedures such as laser resections and stent placement may definitely profit from anxiolytic and amnestic premedication, especially when performed under general anesthesia. In our institution, adults usually receive atropine (0.5–1 mg) and midazolam (7.5 mg) orally 90 min before the intervention, except if at considerable risk for hypoxemia and hypercarbia. Potential alternatives for adults are oral treatment with diazepam (5–10 mg), lorazepam (1–2 mg) or temazepam (15–30 mg). These dosages should be reduced in elderly or debilitated patients.

Monitoring

Adequate monitoring (table 3) is critical to recognize and prevent respiratory or cardiovascular complications [21–23]. Intraoperative monitoring should at least include continuous pulse oxymetry during every procedure that is carried out under sedation [24]. Furthermore, electrocardiography, intermittent noninvasive measurement of blood pressure, capnography and monitoring of neuromuscular relaxation are considered to be minimal standard, if general anesthesia and neuromuscular relaxation are performed. Transcutaneous measurement of PCO_2 and PO_2 [25, 26] are helpful during interventional bronchoscopic procedures, especially when jet ventilation is used. Better hemodynamic surveillance may be achieved by continuous invasive blood pressure monitoring in patients at risk for adverse cardiac events or in the presence of critically narrowed carotid arteries, when hypotension and cerebral hypoperfusion must be avoided. Myocardial ischemia may be detected using computer-

assisted ST-segment analysis, which is nowadays incorporated in most advanced ECG monitors. Patients with severely impaired cardiac function may benefit from insertion of a pulmonary artery catheter allowing to optimize hemodynamics during the intervention and recovery.

Anesthetic Techniques

Local Anesthesia

Topical local anesthesia for flexible bronchoscopy can be achieved using lidocaine applied by nebulizer [27, 28], spray [27], transcricoid injection [29] and via the working channel of the bronchoscope using a 'spray as you go' technique [29, 30]. Application by a nebulizer requires more time than all the other routes, but is favored by patients [27] and results in lower systemic lidocaine levels [31, 32]. Topical local lidocaine applied into the tracheobronchial tree is rapidly absorbed, and therefore, a maximum dose of 4 mg/kg is recommended [32, 33]. A recent report [34] demonstrated plasma levels below 5 μg/ml using higher doses (500–700 mg) of lidocaine, applied topically as a mixture of 2% solution and 2% gel for fiberoptic bronchoscopy. Peak plasma levels occurred 20–30 min after the beginning of topical anesthesia. Signs and symptoms of local anesthetic toxicity are due to central nervous stimulation manifesting as restlessness, hyperactivity, tinnitus, vertigo, seizures, followed by central nervous system depression with slurred speech, mental clouding and loss of consciousness. Hypotension and bradycardia or cardiac arrest are indicative of massive intoxication.

General Anesthesia

Inhalational anesthesia using volatile anesthetics such as halothane, isoflurane or sevoflurane can be performed with the patient breathing spontaneously or controlled through the side-port of the rigid bronchoscope [35, 36]. While these techniques were frequently applied in the past [37, 38] and are still state of the art in neonates and children [35, 36, 39], general anesthesia for adult rigid bronchoscopy is performed using total intravenous anesthesia in most of the recently published studies [40–44].

Our standard general anesthesia technique (table 4) for interventional rigid bronchoscopy is a total intravenous anesthesia, consisting of hypnotic action, analgesia and neuromuscular relaxation. Propofol is a hypnotic drug with good quality of recovery, which is given for induction (1–2 mg/kg) as well as maintenance (6–10 mg/kg/h) of anesthesia. Alternatively, midazolam titrated in 0.05 mg/kg boluses or ketamine (0.5–1 mg/kg) is added. Analgesia and attenuation of cardiovascular responses is provided with intermediate or short acting opioids such as fentanyl, alfentanil or remifentanil. Muscle relaxation performed with succinylcholine, atracurium or mivacurium is usually provided to prevent coughing or bucking with inherent risks of tracheal injury. A recent study prospectively evaluated the safety of intravenous anesthesia and spontaneous assisted ventilation during rigid bronchoscopy with topical anesthesia of the vocal cords and the larynx provided with intense spraying with lidocaine instead of general anesthesia and neuromuscular relaxation [42]. An incidence of 12% reversible perioperative hypoxemic events related to the procedure was noted.

Table 4. Intravenous general anesthesia for interventional bronchoscopy

Effect	Medication
Hypnotic action	propofol, midazolam, ketamine
Analgesia	fentanyl, alfentanil, remifentanil
Muscle relaxation	succinylcholine, atracurium, mivacurium

Ventilatory Support during Flexible Fiberoptic Bronchoscopy

Ventilatory support can be continued in intubated patients through the tracheal tube during flexible fiberoptic bronchoscopy, if an adequate size of the tube has been chosen [45, 46]. Alternatively, a laryngeal mask airway can be used during flexible fiberoptic bronchoscopy in anesthetized [47] and awake adults [48, 49], anesthetized children [50, 51] and neonates [52].

Ventilatory Support during Rigid Bronchoscopy

During rigid bronchoscopy, ventilation may be spontaneous, assisted, controlled (IPPV) or manual by hand bag and performed while high flow of air/oxygen is applied through the side port of the rigid bronchoscope (fig. 2). Alternatively, gas exchange may be achieved by the utilization of high-frequency jet ventilation (HFJV) via a special luer-lock connector at the proximal end of the bronchoscope (fig. 3).

Fig. 2. Rigid bronchoscope (Dumon-Harrel) with a 15-mm side port (1) which can be fitted to a conventional anesthesia circle system enabling regular ventilation. The light source (2) is connected to the telescope lens (3); separate ports (4) for suction catheter and laser probe.

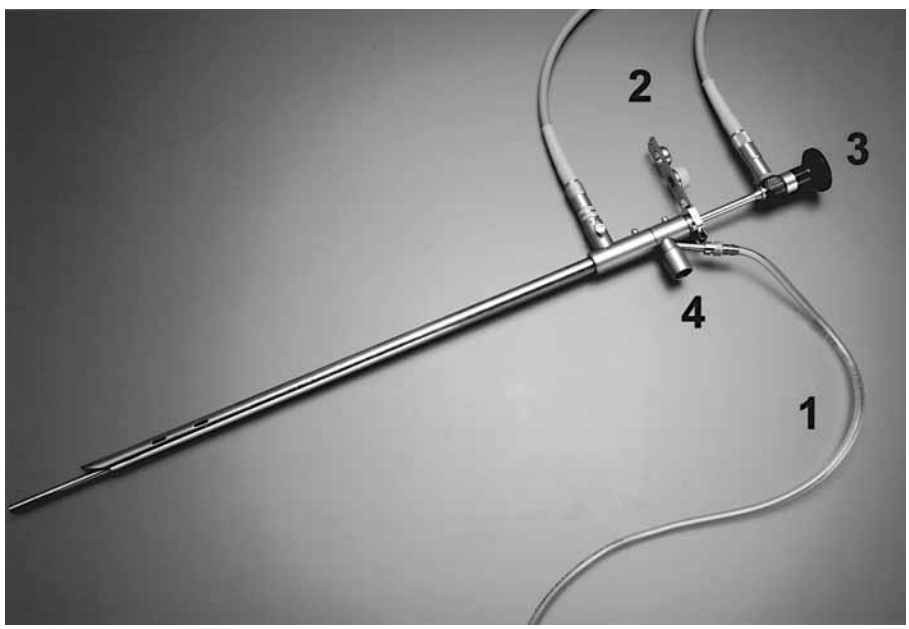

Fig. 3. Rigid bronchoscope (Storz) with a Luer-lock adapter which is directed towards the bronchoscope axis in a 35° angle and connected to the jet ventilator line. Alternatively, the 15-mm perpendicularly positioned side port (4) can be fitted to a conventional anesthesia circle system enabling regular ventilation. Light sources (2) are connected to the bronchoscope as well as to the telescope lens (3).

Spontaneous, assisted, or intermittent positive pressure ventilation through the rigid bronchoscope is easily performed, if inspiratory oxygen concentration can be increased to levels that allow adequate oxygenation. However, if inspiratory oxygen concentration is below 40%, as recommended during laser interventions, hypoxemia may occur, especially if a main bronchus is selectively intubated (fig. 4), and ventilation through the side holes of the bronchoscope barrel is not sufficient [42]. In such situations, cooperation between endoscopist and anesthetist is essential. If desaturation (<90%) occurs, the endoscopist must temporarily interrupt the procedure and pull back the bronchoscope until its tip is located above the main carina to provide bilateral ventilation at increased inspiratory oxygen concentration. Additionally, this allows the endoscopist to inspect the contralateral lung for secretions

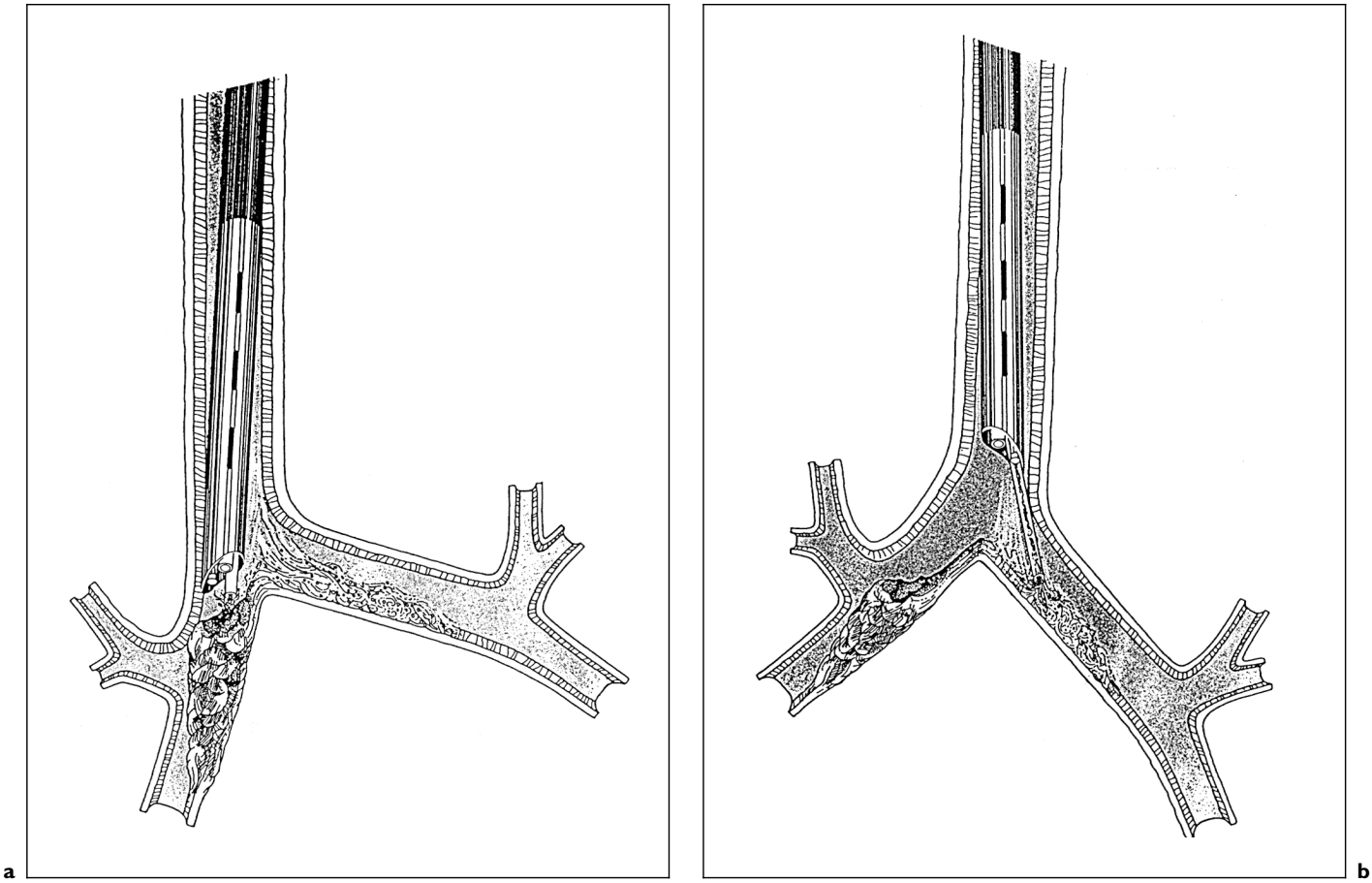

Fig. 4. Schematic representation of a rigid bronchoscope entering the right main bronchus, where an obstructing tumor is located (**a**). Inadequate ventilation and desaturation may occur due to secretions and bleeding into the left main bronchus. Pulling back the bronchoscope above the carina, aspiration of secretions and blood (**b**), and temporary hyperoxygenation usually result in rapid recovery of saturation. Unilateral intubation is reattempted, and the procedure may be continued [reproduced with permission: Dumon JF, Corsini A, Jacomi JP/C (eds): Aspects pratiques de la résection endoscopique au laser en bronchologie. Marseille, Dumon, Corsini & Jacomi, 1988, pp 98–99].

or blood, which might have spilled over inadvertently. Pulling back the bronchoscope above the carina and suctioning secretions or blood (fig. 4) usually results in rapid recovery of the saturation. With a stable saturation of >90% on 40% inspiratory oxygen concentration, unilateral intubation is reattempted and the procedure may be continued.

In critical situations where active bleeding takes place during desaturation, an inflatable ballon or cotton swab drenched in a vasoconstricting solution (epinephrine, vasopressin) can be inserted into the affected bronchus, while the bronchoscope is pulled back and kept above the main carina.

This technique during endobronchial laser surgery may slow down the procedure, but remains a very safe approach by preventing endobronchial fires, which may have devastating consequences with severe tracheobronchial burn injuries.

Jet Ventilation

The application of jet ventilation via rigid bronchoscopes is very convenient, since it offers optimal visibility and easy access for diagnostic and surgical instruments into the airway lumen (table 5). This technique has been introduced into clinical practice by Sanders in 1970 [53], and therefore, to the present time, it is often called Sander's injector technique. Another common denomination

Table 5. Advantages and disadvantages of jet ventilation

Advantages of jet ventilation
Optimal visibility and access to the surgical field
No fire hazard during laser surgery
Lower airway pressure
Effective ventilation in stenotic and/or unsealed airway
Support of mucociliar clearance
Less impairment of hemodynamics in hemodynamically compromised patients
Disadvantages of jet ventilation
More difficult carbon dioxide elimination
More difficult monitoring of carbon dioxide elimination
Less predictable effectivity of gas exchange
Unsuitable for application of volatile anesthetics
Limited efficiency of gas heating and humidification
Hazard of barotrauma if passive gas exhalation is precluded
Higher risk for aspiration of gastric content[1]

[1] If jet ventilation is interrupted or frequency is below 100/min.

is 'Venturi principle', which actually covers only one of the involved mechanisms for gas transport and exchange in the airway.

Most rigid bronchoscopes are equipped with two different connectors (fig. 3) for breathing systems. A 15-mm perpendicularly positioned standard side port can be fitted to a conventional anesthesia circle system enabling regular ventilation, while a Luer-lock™ adapter which is directed towards the bronchoscope axis in a 35° angle is connected to the jet ventilator line. This mode of gas release entrains ambient air through the open proximal end of the bronchoscope, while passive gas exhalation is achieved through both, via the bronchoscope lumen, as well as outside its circumference via the partially open glottis. Side holes down the bronchoscope body allow bilateral ventilation even when the tip of the tube is introduced into one of the main bronchi.

Jet ventilation implies the intermittent insufflation of gas with high pressure through a narrow outlet into the open and unsealed airway [54]. This technique is indicated, either if the utilization of a regular endotracheal tube is not possible (inconvenient or even contraindicated like in the presence of laser surgery), or if the continuity of the airway cannot be maintained during the entire surgical procedure (like during tracheal resection). Another indication derives from the fact that even in high-grade airway obstruction, a sufficient gas exchange may be maintained with jet ventilation [55]. This is the case if the bronchoscope axis is directed towards the remaining airway lumen opening, and the insufflated oxygen is not necessarily conducted by any means of tubing such as a catheter through the stenosis. The applied gas portions are accelerated by the high-pressure gas source and intrude deeply into the tracheobronchial system. If the impulse frequency is lower than 60 cpm, low-frequency jet ventilation is applied, while during ventilation with 60–600 cpm, there is HFJV [56, 57], which is commoner in the operative use of this method. Gas exchange is dependent on several factors which act simultaneously (molecular diffusion, augmented diffusion, Taylor-type dispersion, forced convection, Venturi effect, regular alveolar ventilation) and at the same time counteract the unfavorable factors such as dead space, 'pendelluft' and lung inhomogeneity [58]. This results in the fact that the delivered tidal volume may be as large or even smaller than dead space, and carbon dioxide elimination is still present [59]. Another characteristic feature of jet ventilation is the simultaneous in- and outflow of the insufflated gas instead of the sequential order during conventional respiration and ventilation. The pressure in the jet line has to be high enough to overcome the specifically high resistance of the jet outlet, which in turn can be a narrow cannula, a flexible catheter or a narrow nozzle at the proximal end of a rigid bronchoscope. Intermittent insufflation is generated by a manually or electronically controlled interruption of the pressure-generated jet flow. This driving pressure must be 20–50 times higher than during conventional ventilation (appr. 1.5–4.0 atm). Other parameter settings which may be adjusted in order to achieve ideal gas exchange are inspiratory oxygen concentration (in air), ventilation frequency, inspiration duration, while resulting parameters are gas flow (minute volume), tidal volume and airway pressure. Due to unavoidable air entrainment, the exact magnitude of the resulting parameters is practically unpredictable. This is also true for the inspiratory oxygen concentration, since the delivered oxygen is further diluted by ambient air.

During HFJV, monitoring of gas exchange is more difficult than during conventional ventilation and requires special equipment. While on-line noninvasive monitoring of oxygenation is simply and sufficiently achieved by pulse oxymetry, the assessment of the actual carbon dioxide status and its dynamics is still a challenge. The insertion of an arterial line may not always be indicated or feasible, and capnography either delivers invalid values or requires special equipment. In contrast, modern transcutaneous PCO_2 monitoring allows noninvasive and continuous carbon dioxide surveillance with a fair degree of precision and an acceptable latency period [25].

Postoperative Care

At the end of the surgical procedure, patients may be intubated with a cuffed endotracheal tube until adequate and sufficient spontaneous respiration is established. Alternatively, when spontaneous ventilation can be expected, the rigid bronchoscope can be removed, and ventilation assistance can be given via a face mask or laryngeal mask. All patients are continuously monitored with pulse oxymetry for the following 2–4 h in the recovery room. Following this period, most patients may be transferred to the ward, provided analgesia and coughing is well controlled, gas exchange has normalized to preoperative values and the patients feel comfortable.

Complications

Complications associated with flexible fiberoptic bronchoscopy result from airway obstruction, oversedation and hypoxemia, mechanical trauma (bleeding, pneumothorax) and potentially from local anesthetic toxicity [60, 61]. The overall rate of complications ranges between 0.5 and 6.8% and depends largely on the type of intervention [62]. Recent studies demonstrated significant bronchoconstriction [63] following topical anesthesia, excessive tachycardia and myocardial ischemia [64, 65] as well as cardiac arrhythmias [66] in some patients during flexible fiberoptic bronchoscopy. Occult severe hypercarbia [67] may occur unrecognized.

Rigid bronchoscopy under general anesthesia was reported to be associated with a higher incidence of life-threatening complications than flexible fiberoptic bronchoscopy, mainly due to inadequate general anesthesia and bronchoscopic interventions [68]. Associated cardiovascular and respiratory complications increase with age and duration of the procedure [69]. Short episodes of hypoxemia [42], hypercarbia [40], major hemorrhage and pneumothorax [43] are the most serious complications (table 6). The choice to use flexible fiberoptic or rigid bronchoscopy primarily depends on the personal preferences of the endoscopist. However, the majority of endoscopists who are trained in both techniques favor rigid bronchoscopy instead of flexible fiberoptic bronchoscopy for all difficult or potentially dangerous indications [70]. Under these circumstances, the rigid bronchoscope, being itself a valuable working tool, may better help to provide control of the airway.

Table 6. Complications during laser surgery for central airway obstruction

	Incidence, %	References
Hypoxemia ($SpO_2 < 90\%$)	15–35	38, 42
Hypercarbia ($PCO_2 > 6$ kPa)	2.4–7.1	38, 40
Major hemorrhage	0.4–0.7	41, 43, 44
Pneumothorax	0.3–0.8	42, 43, 44
Mortality	0.45–3.2	38, 41, 43, 44

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Functional Evaluation before and after Interventional Bronchoscopy

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Summary

In this section, an overview of the clinical findings, laboratory investigations and physiology testing and complementary radiographic imaging studies pertinent to the bronchoscopist evaluating patients with presumed central airway obstruction is presented. Although many of these tests may seem superfluous, especially when patients present with life-threatening airway obstruction, others are warranted in order to preserve and maintain the safety profile of bronchoscopic interventions. How these investigations impact interventional strategies, technical success rates, and outcomes is also discussed. Issues requiring further research are also identified.

Despite the widespread utilization of interventional bronchoscopy, standard protocols pertaining to functional assessments of patients before and after these procedures have not been developed. In fact, there has been open debate among specialists in this area as to whether a thorough patient evaluation is even necessary. After all, some argue, many patients referred for emergency procedures have acute, life-threatening central airway obstruction warranting intervention regardless of procedure-related risks, chance for success, overall prognosis or severity of the patient's underlying medical condition.

If this is the case, it is possible that the results of chest imaging and cardiopulmonary physiology studies would be of little value. Inherent procedure-related risks lie, in fact, at the procedural level: that is, what the interventional bronchoscopist can and cannot accomplish with the equipment and instrumentation available in his or her institution. Because many of the classically accepted high-risk factors [1] for surgery, such as forced expiratory volume in 1 s (FEV_1) less than 1,000 ml, hypercapnia, severe exertional dyspnea and advanced age, are frequently encountered in patients referred for therapeutic bronchoscopic interventions, further elucidation of surgical risks and factors potentially affecting outcome are superfluous.

A confounding issue, quite frankly, is that interventional bronchoscopists are often both daring and courageous. Recognizing they represent the last barrier separating patients from death by suffocation, procedures will often be attempted regardless of severity of underlying disease and extent of tracheobronchial obstruction. With increased experience, interventional bronchoscopists learn which lesions are most amenable to technically effective endoscopic treatment, and will therefore turn down selected patients. At the same time, however, the true expert will be capable of taking on increasingly challenging cases, and a patient 'contraindicated' by one interventional bronchoscopist may be relatively straightforward for the expert.

With these issues in mind, the following paragraphs are devoted to a description of the types of patients and situations encountered by the interventional bronchoscopist, a discussion of the potential value of the preprocedure assessment and postprocedure decision making process,

and finally, a review of generally accepted results pertaining to the impact these procedures have on symptom resolution and quality of life, pulmonary function and survival. For the sake of clarity and timeliness, references have been intentionally limited to selected studies published since 1990.

Patient Profiles

The one thing patients referred for interventional bronchoscopy usually have in common is clinically suspected or bronchoscopically evident central airways obstruction. The interventional bronchoscopist's first mission, therefore, is to confirm the appropriateness of the referral. This is not as simple as it initially may appear.

In fact, there is substantial anecdotal evidence that results of imaging and pulmonary physiology studies are unreliable in diagnosing tracheobronchial abnormalities. Often, patients with suspected airway masses on imaging studies have normal-appearing airways on flexible bronchoscopic examination. In addition, the bronchoscopic assessment made by a noninterventional bronchoscopist may be vastly different from that made by the interventionist, raising the delicate question whether all patients, regardless of the results of a previous bronchoscopy, should undergo repeat flexible bronchoscopy by the interventional bronchoscopist (this question will be addressed in greater detail later in this chapter). If one presumes, however, that patients referred for interventional bronchoscopy have central airway obstruction, how might these patients differ, and does it actually matter to the operator?

Acute Airway Obstruction from Malignant Disease

Patients with acute airway obstruction from malignant disease almost always have a known history of cancer. Usually these patients have bronchogenic carcinoma, although other malignancies commonly involve the airways. These include, but are not limited to, melanoma, colon cancer, renal carcinoma, breast cancer, esophageal cancer, thyroid cancer, adenoid cystic carcinoma, carcinoid tumors and sarcomas.

Patients with malignant airway obstruction present acutely when the bulk of their tumor significantly obstructs the tracheobronchial lumen. Although some patients present in this fashion and have no previous histories of cancer, most have undergone systemic or local-regional therapy for their primary neoplasm. Others have known or suspected metastatic disease to other organs, including the lung. Usually, evidence of metastatic disease is visible on body imaging studies. Patients may or may not be receiving systemic therapies.

Symptoms of acute airway obstruction include rapidly increasing dyspnea or tachypnea, cough, hemoptysis, chest pain, hemodynamic instability, respiratory failure, hypoxemia and/or hypercapnia. These symptoms may be associated with acute respiratory failure necessitating intubation, impending respiratory failure, loss of consciousness, altered mental status, depression, failure to thrive, dysphagia or high-grade anxiety.

In my opinion, the purpose of interventional bronchoscopy in most cases of acute airway obstruction from cancer is palliation, not cure. Reestablishment of patent airways may avoid hospitalization in a critical care unit, prolonged intubation and mechanical ventilation, and enhance a patient's ability to accept and undergo systemic chemotherapy, immunotherapy or radiation therapy.

Because some patients with known malignancies present with symptoms requiring emergency intubation or hospitalization, the interventional bronchoscopist must rapidly determine whether temporary reversal of the life-threatening process is possible, and whether the risks potentially related to the procedure are acceptable. Procedures may be required in patients with extensive intraluminal disease with or without associated extrinsic compression. In many instances where patients are referred in extremis, often directly to the operating room or interventional suite, there may not be time for an extensive preprocedure assessment.

Acute Airway Obstruction from Benign Disease

Acute airway obstruction from benign airway disease is usually manifest when the diameter of the tracheobronchial lumen narrows to below a critical level. Unfortunately, there is probably great interindividual variability regarding this critical diameter. In addition, early symptoms may go unnoticed because patients become increasingly accustomed to exertional dyspnea or cough, gradually decreasing their physical activities accordingly. In many of these cases, presenting symptoms include dyspnea at rest or with minimal exertion, hemoptysis or chronic dyspnea and wheezing poorly responsive to bronchodilators and corticosteroids.

Benign diseases causing central airways obstruction include, but are not limited to, adenomas and other benign, often slow growing tumors (such as lipomas and hemartomas), infectious diseases such as tuberculosis, histoplasmosis, coccidioidomycosis, Klebsiella rhinoscleroma, papillomatosis and aspergillosis), postintubation

injuries (fibrous strictures and edema), posttracheostomy injuries (bleeding, fibrous strictures, edema), inhalation, chemical or thermal injury (edema, fibrous strictures, necrotic slough), systemic or local-regional manifestations of illnesses such as Wegener's granulomatosis, amyloidosis, goiter and compressive mediastinal adenopathy, extrinsic compression of the trachea or left main bronchus from an indwelling esophageal stent, post-lung transplantation, foreign body inhalation and, of course, excessive secretions or granulation tissue formation in patients with indwelling airway stents.

Patients with benign causes of airway obstruction may also present in extremis. In my opinion, the interventional bronchoscopist's mission is first to restore airway patency, and second to assess the potential for curative bronchoscopic or open surgical treatment in these patients. Emergency interventional procedures in this setting are usually life saving, allowing patients to calmly participate in subsequent decision making regarding further treatment options.

Serendipitous Finding of Central Airways Obstruction Regardless of Etiology

Patients may be referred to the interventional bronchoscopist for symptoms or radiographic findings that prompt a diagnostic flexible bronchoscopy. During this procedure, central airway obstruction can be discovered. Many patients may be undergoing treatment for presumed gastrointestinal reflux, asthma or recurrent bronchitis. Others will have symptoms presumed to be related to a systemic illness. In some, airway obstruction is not a consideration until offered as a potential explanation of symptoms and findings by the consulting interventional bronchoscopist.

The interventional bronchoscopist is thus placed into a complex and potentially self-serving situation. On the one hand, if airway obstruction is suspected, the interventional bronchoscopist must discover it. On the other hand, this incites the proceduralist to perform potentially unwarranted or unnecessary procedures based on experience, patient and referring physician desires, general index of suspicion, need for increased procedural activity and requirements for budget justification or fiscal reward. Regardless, if airway obstruction is discovered in the otherwise stable and non-life-threatened patient with or without airway symptoms, the interventional bronchoscopist must also determine the appropriateness of additional diagnostic tests before proceeding to a scheduled airway intervention or be able to justify emergency intervention to restore airway patency.

Preprocedure Evaluation

Patient History

A patient history should be a part of any interventional bronchoscopy consultation. If the history cannot be obtained from the patient, it should be obtained from family members, friends or the referring physician. One can argue, of course, that history is unimportant: all that matters is to restore airway patency. This again brings into play the fact that interventional bronchoscopists are, above all, technicians whose first role is to restore and maintain airway caliber. Subsequently, critical care specialists, surgeons, otolaryngologists, anesthesiologists, oncologists and primary care physicians will contribute to maintaining the patient's hemodynamic stability and general medical condition. Using a multidisciplinary approach to complex airway management, the interventional bronchoscopist will be instrumental in developing additional treatment plans.

I believe that patient history can assist the bronchoscopist in determining the chronicity or acuteness of the problem, predict potential risks for recurrent airway obstruction, and provide the bronchoscopist with clues about survivability (performance status, chronicity of the process).

The history, therefore, should include elucidation of symptoms, questions about positional changes affecting cough or dyspnea, localization of chest discomfort in case of hemoptysis, and presence of resting or exertional dyspnea.

The patient should be asked about past medical history including previous cancers, benign systemic illnesses, heart disease (which might influence anesthesia protocols), respiratory disease (history of wheezing, bronchospasm or laryngealspasm), chemo- or radiation therapy, presence of renal failure (patients undergoing renal dialysis may be anticoagulated or be at risk of periprocedure bleeding) and intubation history.

Other questions might be directed towards discovering hoarseness or coughing with deglutition (often indicative of subglottic stenosis, vocal cord paralysis or laryngeal dysfunction), obstructive sleep apnea (excess tissues of the posterior pharynx can make rigid bronchoscopic intubation more difficult), cervical arthritis (also affects rigid bronchoscopic intubation), angina and medication usage (anticoagulants, immunosuppressants, antidepressives, narcotics, antihypertensives, antianginals, antiseizure medications).

Physical Examination

A routine part of any preprocedural evaluation, the physical examination should focus on condition of the teeth (dentures, loose or broken teeth, oral hygiene), evidence of tracheal deviation, focal or diffuse wheezing, ronchi, decreased breath sounds, presence of subcutaneous emphysema, evidence of superior vena cava syndrome such as upper extremity edema and dilated superficial chest veins, heart rate and rhythm and blood pressure. Hypotension, particularly in the elderly, might increase anesthetic risks using propofol and prompts a change in anesthetic management. Obviously, this list is incomplete. Any and all factors that could potentially affect ease of intubation with either an endotracheal tube or a rigid bronchoscope, hemodynamic stability, periprocedural anesthetic management and operative risk should be carefully evaluated.

Chest Imaging Studies

It is rare indeed for the results of imaging studies to affect preprocedural planning or bronchoscopic management. In fact, even the chronicity of atelectasis, once thought to preclude attempts at restoring airway patency, has been disregarded by experienced interventional bronchoscopists. Because the interventional airway procedure is often the only chance patients have at recovering satisfactory airway caliber, many would argue that intervention be attempted regardless of radiographic findings.

To my knowledge, there are no studies demonstrating utility of radiographic studies, and investigators have not examined correlations of radiographic abnormalities with extent of bronchoscopically visualized airway obstruction, discovered extrinsic or exophytic disease or chance for success of interventional bronchoscopy. There is no doubt that studies such as these are difficult to design because of the lack of a common nomenclature describing and grading airway abnormalities, and because diverse interventional procedures (laser resection, stenting, brachytherapy, cryotherapy, electrocautery) are employed. In addition, outcome analysis (measures of success) can pertain to results of follow-up imaging studies, symptom resolution or improvement, technical resolution of the airway obstruction which may or may not be accompanied by symptomatic or functional improvement, survival or change in hospitalization status.

Regardless, the chest radiograph can be reviewed in search of subglottic stenosis, tracheal deviation, reduction of the caliber of the tracheal air column, bronchial air column deviation, volume loss, lung masses, atelectasis, pulmonary infiltrates, postobstructive pneumonia, consolidation, elevation of a hemidiaphragm, pleural or pericardial effusion, mediastinal adenopathy and subcutaneous emphysema. Most operators prefer having a preprocedure chest radiograph available, if only for comparison purposes with subsequent postprocedure studies.

Chest computed tomography (CT) scans, although useful for staging malignant disease, are not absolutely necessary for most therapeutic bronchoscopic procedures. Of course, many would argue that CT measurements are beneficial in patients undergoing expandable or self-expanding metal stent insertion. Neither the accuracy nor the necessity of these measurements have yet been demonstrated by prospective studies. The extent of disease noted on CT scans does not necessarily correlate with what is eventually discovered bronchoscopically. In addition, volume loss, atelectasis and pulmonary infiltrates may resolve once a patent airway is restored. Contrast CT allows better identification of vascular structures in proximity to the airway obstruction, but again, avoidance of these structures and of the potentially lethal consequences in case of laceration or perforation of these blood vessels, is primarily a technical issue (angle of insertion of the rigid bronchoscope, power density used during laser resection, dilatation and stent insertion technique). It is noteworthy, however, that contrast CT can be helpful in identifying neoplastic occlusion of the pulmonary artery, which, in the presence of severe atelelectasis, might suggest that opening of the ipsilateral bronchus is unwarranted. Also, CT scanning might reveal complete obstruction of distal bronchi, particularly of the lower lobe, in patients with a large central obstructing mass. In these cases, it is likely that endoscopic treatment will be unsuccessful and should probably be avoided.

Although magnetic resonance imaging and 3D reconstruction images are beautiful to watch, especially when digital technology allows us to project images over the World Wide Web, their utility has not been demonstrated. For the moment, it is unclear how a 3D reconstruction can replace findings of direct bronchoscopic visualization. I predict, however, that virtual reality reconstructions will eventually allow preprocedure planning, as well as provide interventional bronchoscopists an opportunity to perform a 'practice run' through the procedure itself before taking the patient to the interventional suite.

The utility of the ventilation perfusion lung scan has never been demonstrated, although some suggest these scans can be used to help assess the degree of ventilation and perfusion of the lung distal to the obstructed airway. Hypothetically, a lung that is neither ventilated nor per-

fused would be unlikely to become functional, even if airway patency were restored. To my knowledge, no investigations of this hypothesis have been published.

The issue raised by the availability of imaging studies is again that the more experienced the interventional bronchoscopist, the more likely he or she is to 'attack' even the most involved and potentially dangerous lesions. With experience, one learns which lesions can and cannot be effectively treated. Often, this cannot be determined until the therapeutic procedure has been attempted and the lesion expertly probed with suction catheters, forceps, dilating balloons, pediatric flexible bronchoscopes or other instruments. Eventually, the conscientious interventional bronchoscopist recognizes his or her limitations; defined by technical expertise, anatomic configuration, location of the abnormality and equipment availability (some might argue that certain lesions should not be approached without photocoagulative or stenting capabilities). Ideally, contraindications to the therapeutic procedure can be reliably posed after the assessment bronchoscopy.

Flexible Fiberoptic Bronchoscopy

The bronchoscopic examination is probably the most important component of the pre-interventional bronchoscopy workup. For this reason, many interventional bronchoscopists prefer to repeat the bronchoscopy in order to see with their own eyes, so to speak, the tracheobronchial abnormalities described. Also, this allows the bronchoscopist to elaborate a strategy for the therapeutic procedure to follow.

During this assessment, the location and extent of the obstruction are noted. It is important to determine approximate, if not exact distances from the vocal cords, main carina and take-offs of lobar bronchi. Is the abnormality in close proximity to or surrounded by large vessels? How fragile is underlying tracheobronchial mucosa? Is mediastinal perforation a risk? What is the overall length of the abnormality, and what is the diameter of the stricture? Does the lesion bleed easily? Is it friable, necrotic or grossly hemorrhagic? Is there evidence of extrinsic compression, is the lesion purely exophytic and intraluminal, or is there evidence of mucosal infiltration or extrinsic compression? If stenting is a consideration, is the lesion amenable to a silicone stent, and if so, how long and how wide should that stent be? Sometimes it may be necessary to have stents custom made. Perhaps a nonsilicone stent is being considered. If so, have the benefits, as well as potential drawbacks of these stents been explained to the patient and considered by the physician: what will be the result of excess granulation tissue formation, stent rupture or tracheobronchial wall perforation? Is this a lesion that is likely to respond to stenting or other therapies, and therefore, should a permanent or temporary stent be considered? These are just a few of the issues that must be addressed by the bronchoscopist.

If a decision is made to proceed immediately to a therapeutic procedure without first doing an assessment bronchoscopy, the interventional bronchoscopist risks encountering an abnormality completely different from the one described by the referring physician, encountering an abnormality that does not require therapeutic intervention, encountering an abnormality beyond his or her abilities to repair, and exposing the patient unnecessarily to the costs of laser standby and general anesthesia.

Upper Endoscopy

An upper endoscopy should only be necessary if the patient has esophageal cancer or if there are suspicions of esophageal stenosis (dysphagia, for example) or esphagoairway fistula. In these cases, double stenting should be considered, and in many institutions procedures can be performed sequentially during the same anesthesia if the interventional bronchoscopist and gastroenterologists are collaborating. Some interventional bronchoscopists are trained in both bronchoscopy and upper endoscopy, making the simultaneous evaluation of the airway and the esophagus in these instances much easier.

Pulmonary Function Tests

Pulmonary function testing, especially spirometry and flow volume loops can rarely be obtained in patients referred in extremis. I would argue, also, that diagnosis of airway obstruction is usually based on history, physical examination, chest radiographs and emergent flexible bronchoscopy. The value, therefore, of preprocedure pulmonary function testing outside of research protocols is unclear. Of course, results are used to demonstrate poor airflow, although many patients have impaired baseline ventilatory function that may confound interpretation.

That is not to say that flow volume loops are not occasionally helpful. For example, if patients have the typical picture of fixed airway obstruction (coffin or box appearence to the inspiratory/expiratory limbs of the flow volume curve), tracheal obstruction should be suspected. Patients with central airway obstruction of intrathoracic origin may have a plateau during forced exhalation instead of the normal rise and fall from peak flow. Patients with stridor or suspected extrathoracic obstruction, on the other hand, will have greater flow impairment during inhalation.

It is noteworthy, however, that airflow obstruction at multiple sites can produce atypical flow volume loops, and it is well recognized that patients with chronic obstructive pulmonary disease (COPD) (many patients with central airways obstruction from cancer have underlying COPD) may not have typical flow volume loop abnormalities despite central airway obstruction. [2] In patients with benign causes of central airway obstruction, such as in patients with strictures at the level of a bronchial anastomosis after lung transplantation, spirometric detection of the obstruction may also be difficult. It is presumed that if native lung function is severely impaired, the contralateral main bronchus functions as a single conduit in series with the supracarinal airway [3]. Also, these patients may have combined fixed and dynamic stenosis (from fibrous strictures and associated focal malacia).

Incremental exercise testing in patients with suspected central airway obstruction has a role only in clinical research protocols. It is likely the data obtained will be of poor and incomplete quality in patients with severe tracheobronchial obstruction. In addition, it is unlikely that exercise will be well tolerated. This exposes patients to hypoxemia, bronchospasm and respiratory distress. I believe that the energies wasted by the patient to run on a treadmill or pedal an exercise bicycle are better used to prepare for and undergo an assessment bronchoscopy.

Ancillary Tests

Blood tests should be obtained depending on the requirements of each institution. Usually they can be individualized. Some tests will be requested as part of a diagnostic workup (such as ANCA levels). Others, such as hematocrit and chemistry profiles and platelets, may be desired in patients with cancer. Coagulation profiles are recommended, especially if patients are on anticoagulants. A careful history in these cases is essential. I have frequently seen patients, as well as family members and referring physicians, neglect to mention that the patient is receiving anticoagulants. It is far wiser to discover hypocoagulability before intervention, than to be wondering why the patient's tracheobronchial lesion is oozing relentlessly despite laser photocoagulation. Abnormal bleeding parameters should be reversed by administration of fresh frozen plasma, platelet transfusions or vitamin K. It is noteworthy that many cancer patients may have a history of pulmonary embolus. In these cases, hospitalization, reversal of Coumadin anticoagulation with vitamin K and administration of intravenous heparin (stopped 4 h before bronchoscopic intervention) are probably warranted.

A question that often arises is whether patients should be typed and screened for possible transfusion in case of massive bleeding. It is extremely unlikely that the patient will lose enough blood during a therapeutic bronchoscopic intervention to warrant transfusion. Unfortunately, in the event of massive hemorrhage during the procedure caused, for example, by spontaneous or iatrogenic perforation of a pulmonary artery, large pulmonary vein, inominate artery, aberrant bronchial artery or aorta, patients are likely to expire on the procedure table regardless of whether transfusions are administered.

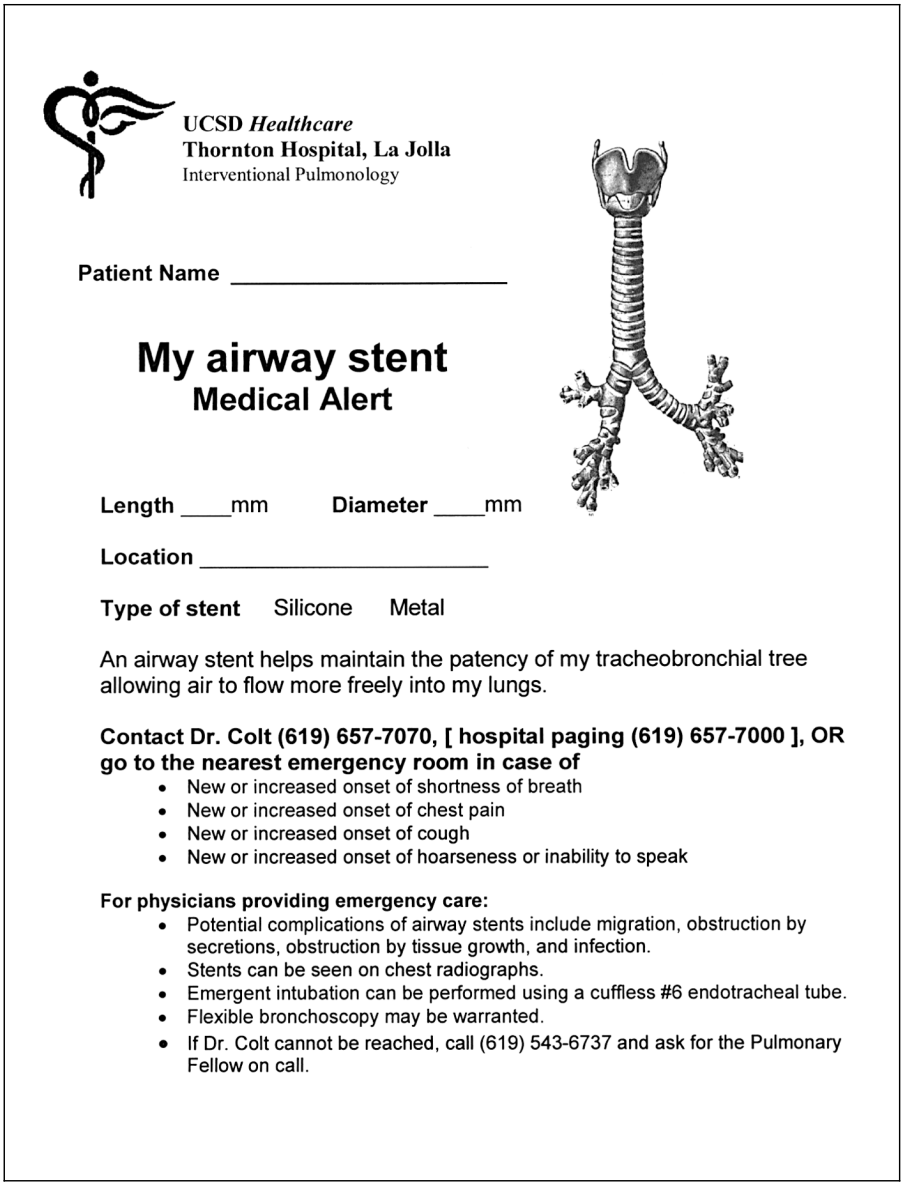
Postprocedure Considerations

Arousal from General Anesthesia or Deep Intravenous Sedation

As a procedure is terminated, the following questions are invariably asked: (1) can the patient be extubated; (2) should the patient receive a bolus of intravenous corticosteroids, and (3) should a chest radiograph be obtained. Interestingly, there are few data supporting answers to any of these three questions.

One suspects that in the absence of a procedure-related adverse event such as substantial bleeding or severe bronchial or laryngeal spasm, patients are almost always extubated after intervention. It is important to realize that once the tracheobronchial obstruction has been treated, patients breath more comfortably, with less effort and have improved oxygenation. One exception to this is the patient who has been tachypneic for many days prior to the procedure, and who may have little or no respiratory reserve. In this case, a short period of positive pressure ventilation can be beneficial. Another exception is the patient presenting emergently and already intubated. In these cases, extubation can and should be considered immediately after the procedure. Often, especially when the obstruction is the result of a benign process, immediate extubation is possible, resulting in lesser hospital-related costs. In patients with malignant airway obstruction, however, extubation may not be possible. In my opinion, this should prompt a discussion about instituting comfort care measures.

The issue of periprocedure administration of intravenous corticosteroids has not been addressed in the interventional bronchoscopy literature. It is common practice to deliver at least one dose of corticosteroids before rigid bronchoscopic intubation. It appears, however, that many operators are beginning to cease this practice, choosing instead to individualize their orders; reserving corticoste-



UCSD *Healthcare*
Thornton Hospital, La Jolla
Interventional Pulmonology

Patient Name _____

My airway stent
Medical Alert

Length ____mm **Diameter** ____mm

Location _____

Type of stent Silicone Metal

An airway stent helps maintain the patency of my tracheobronchial tree allowing air to flow more freely into my lungs.

Contact Dr. Colt (619) 657-7070, [hospital paging (619) 657-7000], OR go to the nearest emergency room in case of

- New or increased onset of shortness of breath
- New or increased onset of chest pain
- New or increased onset of cough
- New or increased onset of hoarseness or inability to speak

For physicians providing emergency care:

- Potential complications of airway stents include migration, obstruction by secretions, obstruction by tissue growth, and infection.
- Stents can be seen on chest radiographs.
- Emergent intubation can be performed using a cuffless #6 endotracheal tube.
- Flexible bronchoscopy may be warranted.
- If Dr. Colt cannot be reached, call (619) 543-6737 and ask for the Pulmonary Fellow on call.

Fig. 1. Medical alert document describing the level of airway obstruction and location of any tracheobronchial stent inserted.

roid use to patients with a history of chronic obstructive airway disease, hyperreactive airway disease, laryngeal spasm, subglottic stenosis or those requiring intubation with a large-diameter rigid bronchoscope. Audible wheezing before or after any procedure will usually prompt administration of corticosteroids and inhaled bronchodilators.

The value of postprocedure chest radiographs is also unclear. If the patient had radiographic evidence of atelectasis, volume loss or pulmonary infiltrates before intervention, a follow-up film may be useful to document resolution of the process after reestablishing airway patency. If, during the bronchoscopy, removal of the airway obstruction resulted in the uncovering and eventual evacuation by aspiration of a large amount of postobstructive mucoid, purulent or bloody secretions, the postoperative film may uncover a new pulmonary infiltrate or spread of an infiltrate to the contralateral lung. In these settings, gram stains, cultures and initiation of appropriate antibiotic coverage are warranted.

Another reason for obtaining postoperative radiographs is to document the absence of procedure-related

adverse events such as pulmonary edema, pneumothorax or pneumomediastinum. If an airway stent was inserted, the postprocedure film will also document stent position and can be compared with films obtained during follow-up visits or future emergency consultations to determine stent migration, recurrent obstruction and atelectasis, or development of a new infectious process.

Hospitalization or Same-Day Surgery

Most patients can be treated and discharged the same day. Practices vary, of course, based on the country of practice, reimbursement incentives and operator biases. Patients with comorbid illnesses are often hospitalized overnight or until their medical problems have been satisfactorily addressed. Patients with poor ventilatory reserve warrant hospitalization for observation. Also, patients with severe subglottic stenosis may also warrant a period of observation, because procedure-related laryngeal spasm is not always immediate. Patients with stents placed in their subglottis are at risk to the consequences of stent migration. These include hoarseness, laryngeal edema, chronic aspiration, recurrent stenosis and respiratory distress, severe cough, dyspnea and stridor.

The appropriateness of hospitalization or same-day surgical practice for interventional bronchoscopic procedures has not been clearly addressed by scientific studies. To my knowledge, no standard of care pertaining to postprocedure management of the patient with treated central airway obstruction has yet been established.

Discharge Planning

If the patient is medically stable, breathing comfortably, has satisfactory oxygenation, heart rate and blood pressure, and no new pulmonary infectious process is suspected, discharge can be considered. Instructions in case of emergency should be explained. I provide patients with a medical alert document describing the level of their airway obstruction and location of any tracheobronchial stent inserted (fig. 1). This document can be folded and plastified to fit into a wallet or purse. A copy of the alert document is sent to the referring physician.

Follow-up outpatient visits are usually scheduled with the patient's referring physician, and with the interventional bronchoscopist. The timing of these follow-up visits, future chest imaging studies or flexible fiberoptic bronchoscopies for surveillance can and should be individualized. To my knowledge, despite a common practice worldwide of performing frequent follow-up flexible bronchoscopic examinations after interventional bronchoscopic treatment, the role for surveillance bronchoscopy in patients with obstructive airway lesions treated by bronchoscopic resection or stent insertion has not been investigated.

Impact of Interventional Bronchoscopy

Studies devoted to determining the impact of interventional bronchoscopy are, for the most part, case series performed in institutions with experiences in either brachytherapy, laser resection or stent insertion. Major flaws of several of these studies are poor study design, substantial numbers of patients lost to follow-up, simultaneous study of patients with benign and malignant obstructive airway abnormalities, and imprecise elucidation of outcome measures.

It is likely, however, that many of the conclusions drawn from these studies are generalizable to most patients with central airway obstruction. Although prospective studies are desperately needed to determine the appropriate indications for each interventional bronchoscopic procedure, there is no doubt that restoring central airway patency results in improved lung function and quality of life for patients with either benign or malignant disease.

Survival, on the other hand, is generally poor in patients with cancer. In these instances, successful restoration of airway patency allows patients to die of the systemic effects of their neoplasm, rather than from gradual or acute suffocation. Demonstrating the benefit of interventional bronchoscopy in these instances is difficult. Today, most would agree that a randomized study of interventional bronchoscopy using a no treatment arm as a control is unethical.

In the following paragraphs, I will briefly describe the major findings of studies performed in the last few years in which outcome measures pertaining to symptoms, quality of life, pulmonary function and survival were succinctly reported. Methodologies used in these studies, many of which are retrospective reviews, vary greatly, making a meta-analysis of the subject both difficult and potentially quite limited.

Effect of Interventional Bronchoscopy on Dyspnea, Other Symptoms and Quality of Life

Immediate symptomatic relief was demonstrated in 83 of 86 patients requiring bronchoscopic intervention for either benign (35 patients) or malignant (51) lesions [4]. Pierce et al. [5] had previously shown that symptomatic improvement had failed to occur following laser resection

in only 3 of 28 patients, although mean time to retreatment or death was only 72 days. Symptomatic improvement has also been shown to occur in 77% of patients undergoing expandable metal stent insertion [6], and in 76% of patients undergoing high-dose intraluminal brachytherapy for endobronchial malignancies [7].

Mehta et al. [8] found that of a total of 166 symptoms present in a group of 52 patients undergoing endobronchial radiation therapy, 131 symptoms resolved and approximately 70% of a patient's lifetime was rendered symptom improved. In another study, Bolliger et al. [9] reported that dyspnea indices and Karnofsky performance status scores improved most significantly one day after insertion of polyurethane-covered Wallstents compared to preinsertion measurements. Additional statistically significant differences at 30 and 90 days after stent insertion were not noted.

Impact of Interventional Bronchoscopy on Pulmonary Function

Not surprisingly, ventilatory function improves in many patients once patency of a central airway has been restored. In a study of 9 patients undergoing metal stent insertion for benign etiologies, Eisner et al. [3] demonstrated mean improvements of 388 ml for forced vital capacity (FVC), peak expiratory flow (1,288 ml), and FEV_1 (550 ml) compared to prestent insertion values. Gelb et al. [10] had previously demonstrated improvements in lung function in 17 patients. This study involved patients with either metal or silicone stents. Mean FVC increased from 64 to 73% predicted, and FEV_1 increased from 49 to 72% predicted.

Vergnon et al. [11] demonstrated that improvements in lung function after silicone stent insertion occurred in greater amplitude in patients with intrathoracic or extrathoracic tracheal airway flow obstruction than in patients with only bronchial obstruction. Improvements in FEV_1, peak expiratory flow, forced inspiratory volume and airway resistance occurred without any significant variation in either forced vital capacity or total lung capacity.

Oxygenation status has also been shown to improve following stent insertion. Hauck et al. [12] reported an increase in Pa_{O_2} from 65 to 71 mm Hg ($p < 0.01$) in a group of 10 patients after insertion of nitinol or Strecker stents, and Jack et al. [13] showed a significant improvement in Pa_{O_2} from 8.6 kPa to 10 kPa in a group of 30 patients also requiring metal stent insertion.

Impact of Interventional Bronchoscopy on Survival

Survival, often used as an outcome measure after therapeutic bronchoscopic interventions, is often discouraging, particularly in patients with cancer. In fact, most studies demonstrate relatively poor survival, regardless of whether patients undergo brachytherapy [14–16], laser resection [17, 18], or stent insertion [19].

Median survivals varying from 2 to 9 months, however, have been reported. In one study, the 30-day mortality was as high as 17% [20], suggesting that although palliative treatment may be warranted in patients with malignant airway obstruction, especially in patients presenting in extremis, it is important that bronchoscopists recognize that overall long-term outcome will often be unsatisfactory, and that many procedures may even be unwarranted.

These concepts were additionally investigated by two separate investigators. In 1993, in a study of laser resection in 17 patients requiring mechanical ventilation for respiratory failure from malignant airway obstruction, bronchoscopic intervention allowed removal from mechanical ventilation and extubation in 9 (53%) patients [21]. The authors suggested that bronchoscopic evaluation should be considered in all patients with respiratory failure from cancer, and concluded that laser resection can be successful for removing patients from mechanical ventilation if an endobronchial abnormality is seen, can be satisfactorily treated, and if the abnormality is the principle cause of the patient's respiratory failure.

In 1997, this hypothesis was taken one step further [22]. This was a study of 32 patients with respiratory failure (18 with benign lesions, 14 with bronchogenic carcinoma) requiring hospitalization in an intensive care unit, and referred for emergent rigid bronchoscopic intervention with laser or stent insertion. Bronchoscopic treatment resulted in removal from mechanical ventilation in 19 patients, and prompted an immediate decrease in the level of care (transfer from the ICU to the wards) in 63% of patients overall. Outcomes were least satisfactory, however, in cancer patients with respiratory failure. In these cases, the authors suggested that although it may be reasonable to attempt bronchoscopic intervention, therapy, if unsuccessful, should incite physicians to discuss institution of comfort care measures with patients or families. On the other hand, in patients with benign disease and central airway obstruction, rapid referral for bronchoscopic intervention will result in less need for mechanical ventilation, decreased stay in the intensive care unit and hospital, and consequently, lesser charges related to health care.

Conclusions

As interventional bronchoscopy moves towards becoming a specialty in its own right, it is essential that global leaders in the field work together to develop standard approaches to the preinterventional evaluation. These tests and procedures will allow better selection of patients for particular interventions, and potentially, better predictions of outcomes.

In addition, standard protocols, decision trees and management algorithms need to be developed and investigated as they pertain to many postintervention issues (a potential example is proposed in the chapter on multimodality treatment of advanced pulmonary malignancy by Bolliger). Studies of outcome measures, in addition to survival, should be well designed and implemented so that practitioners can further justify the performance of these expensive, but often life-saving procedures to hospital administrators who are often unwilling to invest in the necessary equipment, as well as to physician groups and third party payers who may be reluctant to approve patient referrals because of cost-of-care concerns.

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Transbronchial Needle Aspiration of Central and Peripheral Lesions

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Summary

Transbronchial needle aspiration (TBNA) is a modality that allows us to sample tissue from the deeper submucosa as well as from the close extraluminal areas of the endobronchial tree. Tissue can be obtained for either cyto- or histological examination, and the diagnosis of malignant as well as benign conditions, including mycobacterial infection can be made, increasing the yield of the flexible bronchoscopy. The procedure reduces need for mediastinoscopy, and in some cases that for thoracotomy, improving patient welfare and reducing cost of the medical care. Despite its proven value, the modality remains underutilized by the modern day bronchoscopists. In this chapter, we provide an up-to-date review of the TBNA literature and discuss reasons for perceived concerns, indications, the technique itself and precautions against damage to the flexible bronchoscope. We believe that the reader of the chapter would get a better understanding, greater confidence and improved yield related to this important diagnostic tool.

Merely a curiosity at inception, today flexible bronchoscopy has emerged as an essential diagnostic and therapeutic modality for a variety of lung diseases. The addition of transbronchial needle aspiration (TBNA) has not only improved its diagnostic yield, it has further extended its role in the evaluation of mediastinal pathology, and the diagnosis and staging of bronchogenic carcinoma (BCa). Aspiration of mediastinal lymph nodes was initially described by Schieppati [1] in 1949 and was subsequently evaluated by European investigators [2–5]. Initially performed through the rigid bronchoscope, it was in 1983 that Wang and Terry [6] first described the procedure of TBNA for mediastinal lymph node sampling, using the flexible bronchoscope (FB). Subsequent publications highlighted its utility in the diagnosis of endobronchial and peripheral lesions [7–9] and the ability of TBNA to provide a diagnosis even in the absence of endobronchial disease, in a nonsurgical fashion, confirmed its usefulness to bronchoscopists [10–12]. In this chapter, we review the role of TBNA in the management of central and peripheral lesions and address the anatomical and technical considerations essential to the TBNA procedure.

Anatomical Considerations

Prior to TBNA of mediastinal lesions, it is essential to have a clear understanding of the relationship of the tracheobronchial tree to surrounding lymph nodes and major vascular structures to allow safe sampling [13, 14]. The needle must reach the core of the lymph node to obtain an adequate specimen while avoiding nearby vascular structures.

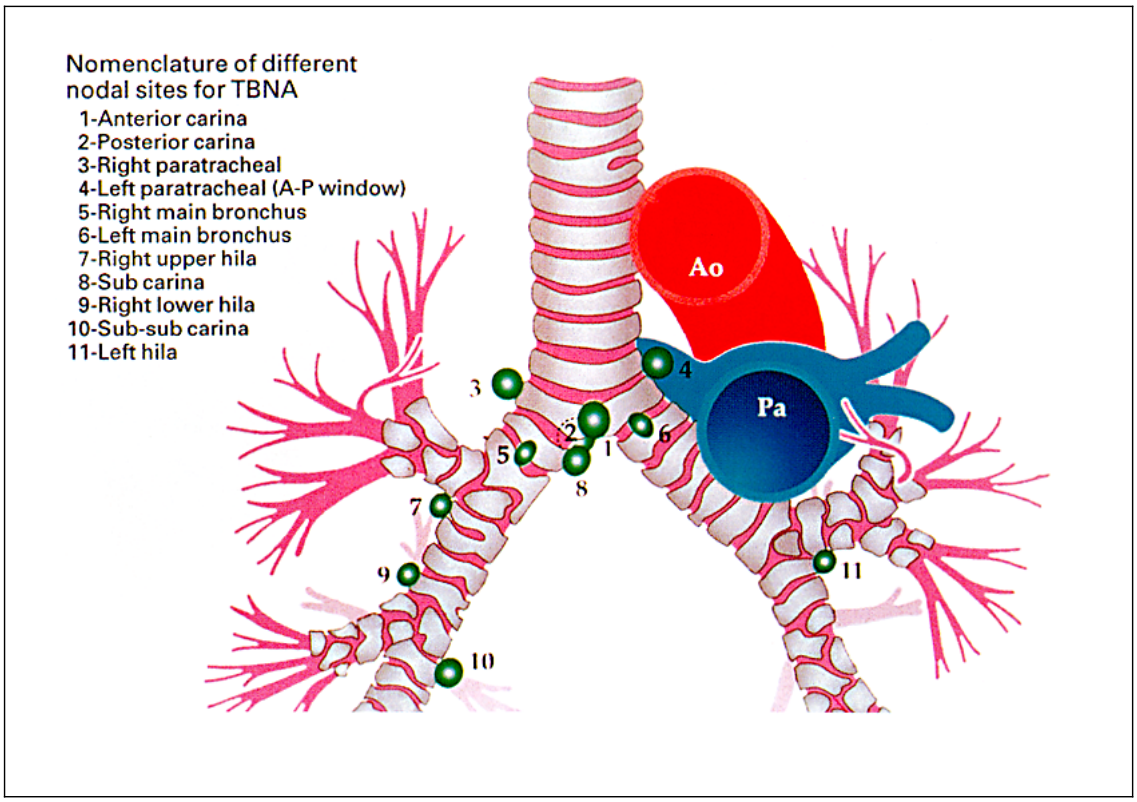

Fig. 1. Schematic diagram of 11 nodal stations accessible to TBNA, as described by Wang [14]. Positive aspiration of stations 1–4 and 8 could impact surgical management of the lung cancer. Ao = Aorta; Pa = pulmonary artery.

Anteriorly and to the right of the distal third of the trachea are found the superior vena cava and azygos vein. Directly anterior to the trachea, above the level of the primary carina, lie the innominate artery and the aortic arch. They cross the origin of the left main stem bronchus and then lie anterior and to the left of the distal third of the trachea making an easily recognizable pulsatile imprint [13]. The main pulmonary artery divides into the right and left branches within the concavity of the aortic arch. The left pulmonary artery runs anterosuperiorly, in close approximation (3–5 mm) with the left main bronchus, while the right pulmonary artery lies anterior to the right main bronchus and the origin of the upper lobe bronchus. The esophagus lies in close approximation (2–3 mm) with the posterior wall of the trachea and the left main bronchus [15]. While performing TBNA, these areas should be avoided unless a clear-cut pathologic process is documented by radiologic evaluation.

Of the 11 nodal stations accessible to TBNA, aspiration of only 5 stations is useful for staging of BCa (fig. 1) [14, 16]. Aspiration of the remaining is to improve the diagnostic yield of the procedure. The location of the lymph nodes in relation to the tracheobronchial tree is best visualized by imagining the interior of the airway as a clockface and using the carina as a reference point. With the bronchoscopist standing behind the patient in the supine position, the subcarinal nodes (ATS station 7) are easily accessible from a point 3–5 mm below on either side of the primary carina, with the needle pointed in an inferomedial direction. Direct puncture of a normal-looking carina is usually avoided. The right paratracheal lymph nodes (ATS station 4R) are best sampled 2 cm or from the second or third intercartilaginous space proximal to the carina at 1–2 o'clock position, avoiding the mediastinal reflection of the pleura and the azygos vein at the 3 o'clock position (fig. 2) [13, 17]. The aortopulmonary window or left paratracheal nodes (ATS station 4L) are best sampled from the lateral wall of the left main bronchus at the level of the carina at the 9 o'clock position. The right hilar nodes (ATS station 11R) are best approached through the bronchus intermedius at the 3 o'clock position, just below the level of the right upper lobe bronchus,

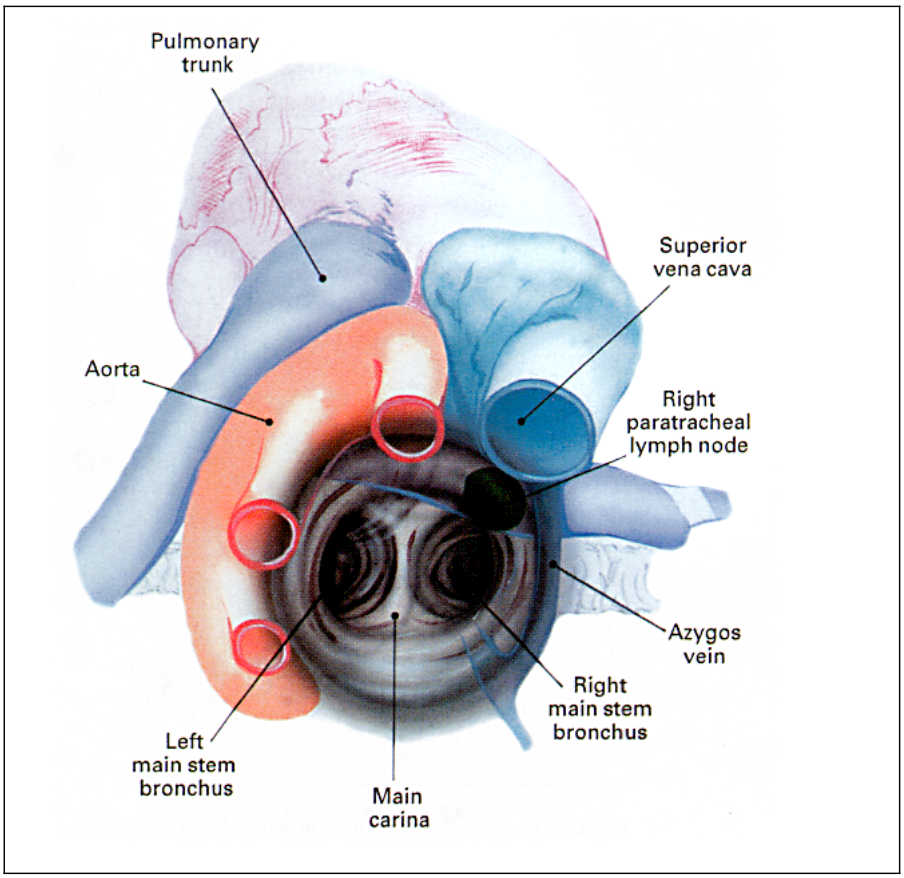

Fig. 2. Schematic diagram depicting usual location of the right paratracheal lymph nodes (see text).

or proximal to the origin of the superior segment of the right lower lobe bronchus [18]. The left hilar nodes (ATS station 11L) may be approached at the origin of the left lower lobe bronchus at the 9 o'clock position.

Technical Aspects

Equipment

All needle systems for transbronchial aspiration consist of: (1) a retractable sharp beveled flexible needle, (2) a flexible catheter and (3) a proximal control device to manipulate the needle, the stylet, or both, and a sideport through which suction can be applied [19]. Due to the wide variety of needles available, we would recommend familiarizing oneself and the support staff with only 1 or 2 needles for each indication. For lesions located outside the airway wall, the needle should be at least 10 mm in length. The 20- to 22-gauge needles are usually used to obtain cytology specimens [19, 20] while the 19-gauge needles are needed to obtain a 'core' of tissue for histology [19, 21]. Due to the nature of the procedure, the catheter used should be flexible enough to be maneuverable into more peripheral locations yet stiff enough to exert force to penetrate the thick proximal bronchial wall for the central lesions. A metal stylet provides the necessary stiffness to the flexible catheter. A needle, 15 mm in length and 21-gauge in diameter is necessary for the aspiration of a mediastinal abscess or cyst. Since nonretractable needles may damage the working channel of the bronchoscope, only retractable needles should be used.

Histology specimens are commonly obtained using the MW-319 histology needle (Mill-Rose Lab Inc., Mentor, Ohio, USA). It is a dual needle system involving 21- and 19-gauge bevelled, retractable needles [19]. The 21-gauge, 5-mm-long needle behaves as a trocar for the 19-gauge, 15-mm-long needle. The former also prevents inadvertent puncture of the major vessels by the latter.

Procedure

It is not necessary to obtain a coagulation profile on a routine basis, in the absence of a history of a bleeding dia-

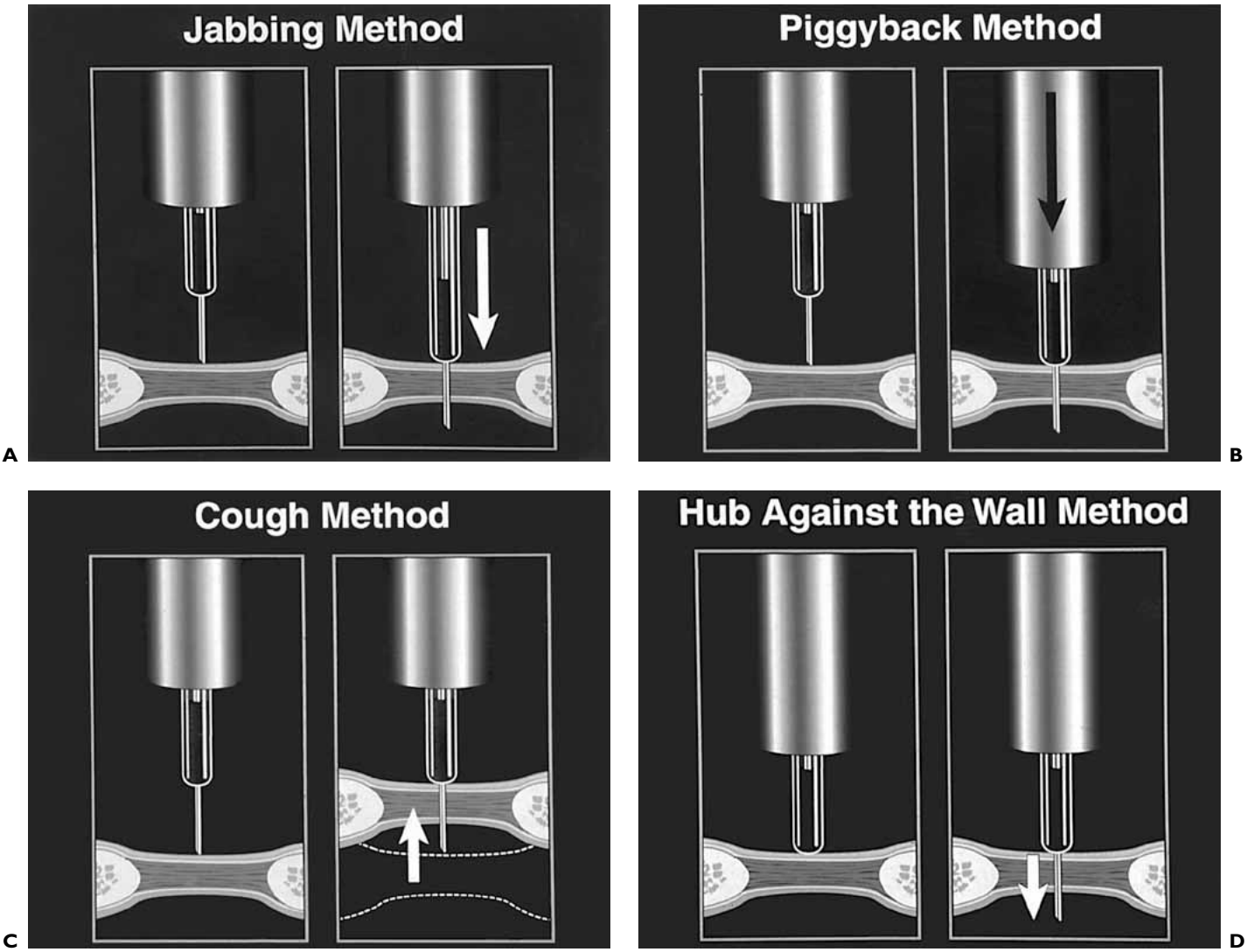

Fig. 3. Schematic diagram of different techniques used for tracheobronchial wall penetration by TBNA. **A** Jabbing method. **B** Pushing or piggyback method. **C** Cough method. **D** Hub against the wall method [19].

thesis [22]. Selection of the proper site for needle insertion to increase diagnostic yield may be facilitated by reviewing the computed tomographic (CT) scan of the chest. TBNA can be safely and successfully performed for unexpected endobronchial lesions encountered during routine flexible bronchoscopy. Fluoroscopy is invaluable and should routinely be used for sampling peripheral lesions.

To prevent damage to the working channel of the FB by the needle, the FB should be kept as straight as possible, with its distal tip in the neutral position during catheter insertion. The bevelled end of the needle must be secured within the metal hub during its passage through the working channel [23]. The needle is advanced and locked in place only after the metal hub is visible beyond the tip of the FB. The catheter can then be retracted keeping the tip of the needle distal to that of the FB. The FB is then advanced to the target area, and the tip of the needle is anchored in the intercartilaginous space in an attempt to penetrate the airway wall as perpendicular as possible. We recommend against protruding the catheter beyond the FB, as this may kink the catheter leading to difficulty in proper needle position, penetration and aspiration. Using the working channel to splint the distal end of the catheter further facilitates sampling.

The following techniques may be used to insert the needle through the airway wall (fig. 3): (1) 'Jabbing meth-

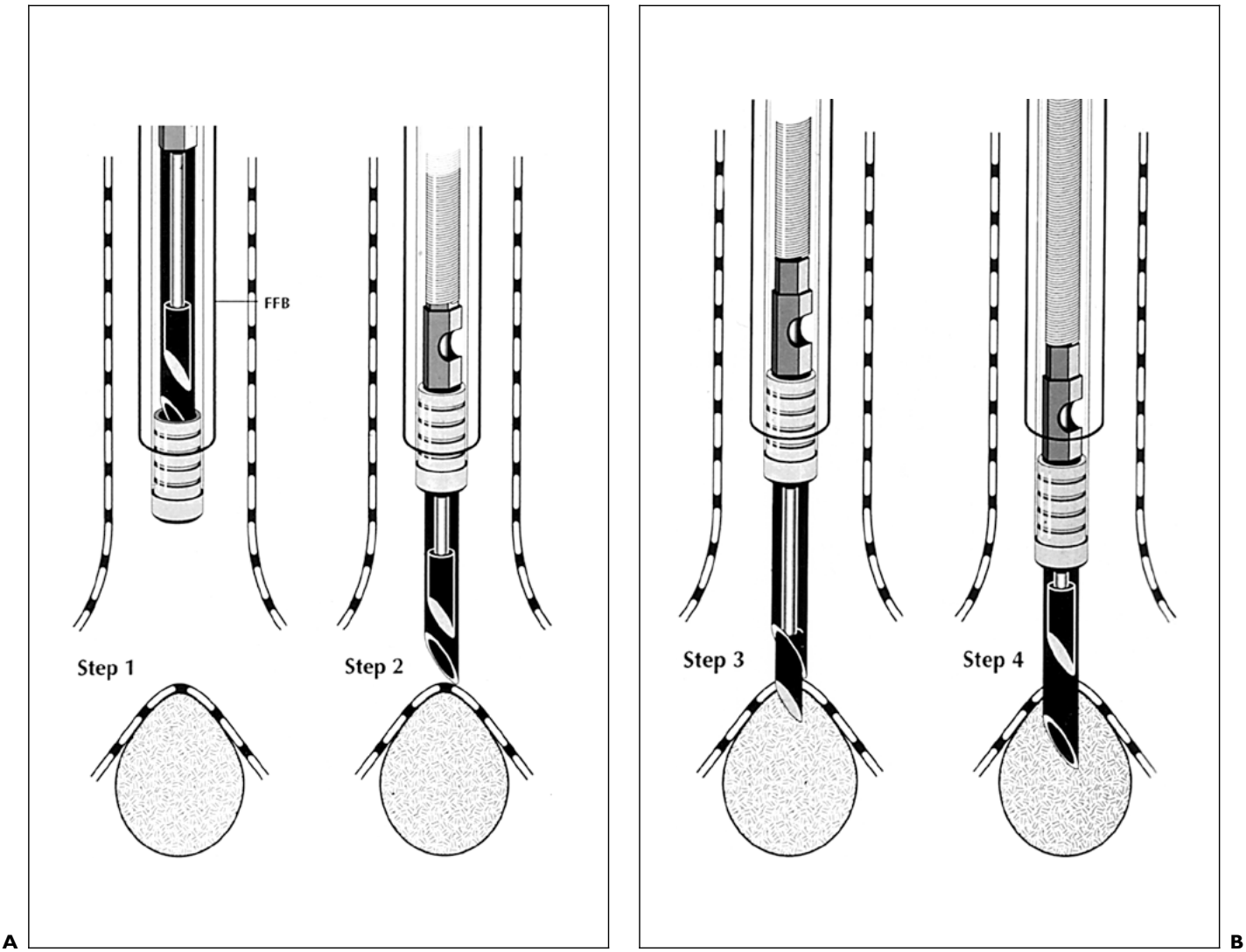

Fig. 4. Schematic representation of histology specimen retrieval by 19-gauge TBNA. **A** Steps 1 + 2. **B** Steps 3 + 4. Reproduced with permission [26].

od': the needle is thrust through the intercartilaginous space with a quick, firm jab to the catheter, while the scope is fixed at the nose or mouth; (2) 'hub against the wall method': with the needle in the retracted position, the distal end of the catheter (the metal hub) can be placed directly in contact with the target and held firmly while the needle is pushed out of the catheter for its spontaneous penetration through the tracheobronchial wall; (3) 'piggyback method': once the needle is advanced and locked in position, the catheter is fixed against the proximal end of the insertion port, using the index finger in a single port scope or the little finger in a dual port scope, to prevent recoil when resistance is met; the bronchoscope and catheter are then pushed forward as a single unit, until the entire needle penetrates the tracheobronchial wall; (4) 'cough method': while applying the jabbing or piggyback technique, the patient is asked to give a hard cough for the spontaneous penetration of the needle [24]. All of these techniques can be used alone or in combination for successful penetration of the needle through the tracheobronchial wall.

With the needle inserted, suction is applied at the proximal sideport using a 60-ml syringe. Aspiration of blood indicates inadvertent penetration of a major intrathoracic vessel, suction is released, the needle is retracted, and a new site is selected for aspiration. When there is no blood

in the aspirate, the catheter is agitated to and fro, with continuous suction, in an attempt to shear off cells from the mass or lymph node. The needle is withdrawn from the target site after releasing suction. The tip of the FB is straightened and the needle assembly is pulled out of the FB in a single, smooth motion. Sampling of peripheral lesions is best performed by placing the metal hub of the needle against the lesion, under fluoroscopic guidance, before pushing the needle into the lesion. For lesions more difficult to reach, the needle may be advanced in a major airway and then guided into the lesion under fluoroscopy. Sampling of endobronchial lesions may be performed by embedding the needle in the lesion, to the metal hub, parallel to the airway wall, and agitating to and fro repeatedly, with continuous suction. Submucosal lesions may be sampled by incomplete penetration of the airway wall at an acute angle, with suction. Proper handling of the obtained specimen is a crucial and underappreciated aspect of the procedure. The specimen for cytology is prepared by using air from a 60-ml syringe to 'blow' the specimen onto the slide (smear technique) [25] before smearing it using another slide and immediately placing it in 95% alcohol. Delay of even a few seconds may result in drying artifacts on the cells. The specimen is then flushed from the needle using 3 ml of saline or Hank's solution and sent to the cytology lab for processing (fluid technique).

The technique of obtaining a histology specimen via TBNA requires use of the 19-gauge needle assembly and is a variation on the technique used to obtain cytology specimens. Before inserting the needle assembly through the working channel of the FB, ensure that the 21-gauge needle is inside the 19-gauge needle which should be inside the metal hub (fig. 4A, Step 1). The assembly is passed through the FB until only the distal metal hub is seen beyond the tip of the FB, taking the same precautions as with the cytology needle. Once the metal hub is visible beyond the tip of the FB, the 19-gauge needle is advanced beyond the metal hub and locked in place (fig. 4A, Step 2). The automatically advanced 21-gauge needle is used to puncture the airway wall and anchored at the target site using any of the techniques previously described (fig. 4B, Step 3). The 21-gauge needle acts as a trocar for the 19-gauge needle and prevents its plugging by bronchial wall tissue. Using a 60-ml syringe containing 3 ml of normal saline solution, suction is applied at the proximal port to ascertain the safety of the location. This is followed by the insertion of the 19-gauge needle to its fullest extent (fig. 4B, Step 4). Under continuous suction, the 19-gauge needle is moved to and fro, partially, 4 to 5 times, to obtain a core of tissue. The needle is flushed into the preservative, to obtain the specimen, although on occasion the 21-gauge needle may be required to push the core out of the 19-gauge needle. Successful sampling is indicated by visualizing a definite core of tissue at the bottom of the preservative container. The specimen is sent for cell block preparation which provides either cytologic or histologic examination, depending on its size and integrity [26]. At least two satisfactory core specimens are obtained at each location, and multiple passes may be required for this [27]. Rapid on-site evaluation of the specimen by the cytopathologist for sample adequacy has been shown to increase diagnostic yield [28]. Table 1 lists some of the criteria that may be used to judge the 'adequacy' of a sample obtained for cytology. Samples containing rare malignant cells, rather than clumps of malignant cells, should not be classified as malignant and should not be relied upon for a diagnosis [29–32]. Table 2 highlights the steps that may be taken to reduce false positive results and avoid overstaging of BCa.

Table 1. Cytologic criteria for an 'adequate' specimen during TBNA

1	Bronchial epithelial cells should be absent or rare.
2	A preponderance of lymphocytes should be found.
3	Strict criteria for cytologic diagnosis of malignancy should be established and adhered to, and all samples should be classified as negative, suspicious or definitely malignant.
4	Only samples showing no evidence of pathology in the presence of lymphocytes should be considered true negatives.

Table 2. Recommendations to avoid false-positive results

1	The FB should not be connected to the suction apparatus until all TBNA samples have been obtained. The area of interest should be washed with saline or lidocaine, if it is covered with secretions, before needle insertion.
2	The TBNA procedure should be performed prior to airway examination or acquisition of other samples.
3	Lymph nodes denoting worse prognosis should be aspirated first, i.e. N3 before N2 before N1, using the same needle, in patients with multiple sites of nodal involvement.
4	Suction should be released prior to needle withdrawal from the lymph node.
5	Histology specimens should be obtained when appropriate.

Adapted from Dasgupta and Mehta [22]

Clinical Applications and Results

Indications

Table 3 summarizes the indications for TBNA. Although diagnosis and staging of BCa remains by far its commonest application, there is considerable potential for growth in other realms such as endobronchial, submucosal and peripheral lesions. Use of the 19-gauge histology needle, to obtain a core of tissue, allows diagnosis of lymphoma and granulomatous inflammation, where cytology alone is felt to be less accurate.

Table 3. Indications for TBNA

1	Mediastinal and/or hilar lymphadenopathy To establish the diagnosis To stage known or suspected bronchogenic carcinoma
2	Endobronchial lesions Especially in case of necrotic tumor, hemorrhagic tumor or to predict the line of surgical resection (see text)
3	Extrinsic compression of the airway by peribronchial process
4	Submucosal disease
5	Peripheral nodules/masses
6	Follow-up of small-cell tumors, lymphoma
7	Diagnosis and/or drainage of mediastinal cysts and/or mediastinal abscesses

Mediastinal Disease

Staging of Bronchogenic Carcinoma. To provide curative surgical resection for BCa preoperative detection of mediastinal spread is invaluable in patient selection. Positive transcarinal aspirates have been used since the 1960s to assess resectability [12]. Lymph node enlargement on CT scan does not constitute proof of malignant spread, and the options available for lymph node sampling include cervical mediastinoscopy, mediastinotomy and TBNA. TBNA offers the ability to sample lymph nodes on both sides of the tracheobronchial tree, in the same sitting, that are inaccessible to cervical mediastinoscopy and/or mediastinotomy. Demonstration of positive N2 or N3 lymph nodes by TBNA would avoid unnecessary surgical exploration for staging and/or resection, thus preventing morbidity and providing substantial cost savings [15, 17, 18, 26, 33]. There are reports of patients with negative mediastinoscopies found later to have subcarinal and pretracheal tumors, making them inoperable [16, 34], such situations can be avoided by TBNA. Besides permitting the staging of BCa, TBNA often provides the only clue for diagnosis with a single procedure [35, 36]. The sensitivity of TBNA in diagnosing small cell carcinoma is higher than for non-small cell carcinoma [33, 37, 38] and diagnosis of small cell carcinoma would preclude surgical intervention in most cases. TBNA can also be performed in situations where mediastinoscopy is difficult, such as patients with tracheostomy or those with severe cervical deformities.

Identifiable predictors of positive TBNA include: (1) presence of endoscopically visible endobronchial tumor [17, 37, 39], particularly involving the right upper lobe [39]; (2) subcarinal lymph node size greater than 2 cm [39], and (3) carinal involvement (visible tumor, widening or erythema) [17, 36, 37, 39] (table 4). Table 5 depicts diagnostic yield from TBNA staging of lung cancer patients. The addition of CT scanning to identify enlarged lymph nodes could enhance the acquisition of biopsy specimens [36, 41] (table 6); however, a normal imaging study (nodes <1 cm) or a normal-looking carina do not preclude positive aspirates. In our own experience (unpubl.) TBNA of nodes <1 cm were often positive and indicative of mediastinal spread. Even though the positive predictive value of TBNA approaches 100% in most published series, a negative result should prompt further testing since the negative predictive value is low.

Schenk et al. [26] studied the sensitivity of 22-gauge and 19-gauge needles in 55 patients with proven malignant mediastinal adenopathy, for staging of lung cancers. The sensitivity of the 19-gauge needle was statistically higher than the 22-gauge needle ($p < 0.0001$) when compared as a staging tool with the 22-gauge needle; however, combining both 22-gauge and 19-gauge needle aspirations in the same patient provided the best diagnostic yield [26]. The sensitivity of cytological analysis of the flush solution was 64% for the 19-gauge needle and 53% for the 22-gauge needle. In 20 patients, only the 19-gauge needle was diagnostic while the 22-gauge needle was exclusively diagnostic in only 2 patients.. The sensitivity of the combined cytology and histology samples obtained with the 19-gauge needle was higher (86%) than either individual sampling or the 22-gauge needle aspirates. Overall, the 22-gauge needle correctly identified only 29 patients, while the 19-gauge needle correctly identified 47 patients. Our recommendations regarding the use of TBNA for the purposes of staging are outlined in table 7.

Sarcoidosis. The availability of the 19-gauge histology needle has expanded the indications for TBNA to include diseases such as sarcoidosis, in which cytology specimens alone have had limited success. Considering that in the past, patients with negative transbronchial lung biopsy

Table 4. TBNA yield based on endoscopic evidence of carinal abnormality

	Total patients	Carinal abnormality					
		present			absent		
		n	TBNA+	%	n	TBNA+	%
Utz et al. [36]	88	30	13	43	58	19	33
Shure and Fedullo [17]	110	21	8	38	89	8	9
Wang et al. [40]	40	14	10	71	26	9	35
Harrow et al. [37]	465	99	52	53	366	105	29
Total	703	164	83	51*	539	138	26*

* $p < 0.001$ (χ^2). Reproduced with permission from Dasgupta and Mehta [22].

Table 5. TBNA for staging of lung cancers as reported in the literature

Authors	Patients with proven CA	Patients with proven mediastinal disease	Positive TBNA	Comments	PPV
Wang and Terry [6]	10	6	5 (83)	1 SMCC	100
Wang et al. [40]	40	25	19 (76)	3 false +; all SMCC	100
Schenk et al. [41]	88	44	19 (43)	2 false +	89
Schenk et al. [42][1]	25	25	20 (80)		100

Figures in parentheses are percentages. [1] 18-gauge needle TBNA for histologic analysis. SMCC = Small cell carcinoma; PPV = positive predictive value; CA = carcinoma. Reproduced with permission from Dasgupta and Mehta [22].

Table 6. TBNA yield based on evidence of mediastinal adenopathy by imaging techniques

	Mediastinal adenopathy			
	present		absent	
	patients	TBNA+	patients	TBNA+
Utz et al. [36]	67	29 (43)	21	2 (10)
Shure and Fedullo [17]	12	2 (17)	98	14 (14)
Shields et al. [43]	2	2 (100)	13	1 (8)
Schenk et al. [41]	44	19 (43)	0	0 (0)
Harrow et al. [37]	124	52 (42)	176	17 (10)
Total	249	104 (42)*	308	34 (11)*

* $p < 0.001$ (χ^2). Figures in parentheses are percentages. Reproduced with permission from Dasgupta and Mehta [22].

Table 7. Recommendations for the routine performance of TBNA

1 All patients presenting with mediastinal or hilar adenopathy or both should have 22- and/or 19-gauge needle TBNA performed as the initial procedure. These results should provide a diagnosis of both malignant and nonmalignant diseases, as well as help in the staging of lung cancers.
2 In patients with visible endobronchial disease, 22-gauge needle TBNA should be performed in case of a necrotic or a hemorrhagic tumor, or in a patient with a bleeding diathesis.
3 All patients with evidence of submucosal and peribronchial disease should have 22-gauge needle cytology sampling.
4 TBNA should be the initial diagnostic procedure in all patients with type 3 and 4 peripheral lesions.

Adapted from Dasgupta and Mehta [22].

were referred for mediastinoscopy, the availability of TBNA provides a less invasive, safe and economical means for obtaining a pathologic diagnosis. Morales et al. [41], in a study of 51 consecutive patients, found that although the TBNA, through a 19-gauge needle, was less sensitive than transbronchial lung biopsy alone, the addition of TBNA increased the diagnostic yield from 60% to 83% for stage I and from 76 to 86% for stage II disease when compared; 23% of stage I and 10% of stage II patients were diagnosed only by TBNA increasing the overall yield of flexible bronchoscopy to 84%. Pauli et al. [45] found that the yield increased to 78% when TBNA was combined with forceps biopsy. They identified noncaseating granulomas in 66% of 193 patients with suspected sarcoidosis, irrespective of the stage of the disease. Using the 18-gauge needle through the FB, Wang et al. [46], showed noncaseating granulomas in 18 of 20 (90%) patients with sarcoidosis. TBNA was the only diagnostic technique in 6 patients who also had other diagnostic procedures performed. They felt that the high sensitivity was due to the fact that the granulomas are more densely packed in lymph nodes than in lung tissues.

Infections. The literature reveals several anecdotal reports of infections diagnosed via TBNA (see below). Diagnosis of mediastinal mycobacterial adenitis (both *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare)* has been described using TBNA in immunocompetent as well as immunocompromised patients [21, 47–53]. TBNA has also been involved in the diagnosis of histoplasmosis [21], pneumocystis carinii pneumonia [21] and cryptococcal infection in patients with AIDS [54]. A recent report by Harkin et al. [55] highlights the usefulness of this technique in patients with HIV disease. Forty-one HIV-positive patients with intrathoracic adenopathy of unclear etiology underwent 44 TBNA (19 G) procedures. Of 23 procedures performed on patients subsequently shown to have mycobacterial disease, aspirations showed smears positive for AFB in 11 (48%), 14 (61%) specimens grew mycobacteria in cultured material, and caseous necrosis or necrotizing granulomatous lesions were seen in 15 (65%). In 11 of 23 procedures (48%), TBNA was the exclusive means of diagnosing mycobacterial disease. No major complications were reported. The report found TBNA to be less successful in patients with lymphoma and Kaposi's sarcoma. Further, larger studies are needed to better define the place of TBNA in patients with HIV disease.

Miscellaneous. Submucosal needle aspiration proximal to an endobronchial tumor to detect local spread may help predict the line of surgical resection in patients with non-small cell carcinoma [56]. It bears emphasizing that in patients with a bleeding diathesis, where mediastinoscopy is contraindicated, TBNA may provide the only means for diagnosis [57]. The clinical utility of TBNA in the diagnosis of lymphoma has been somewhat limited since this usually requires larger samples of nodal tissue than are normally obtained by the 22-gauge needle. The appearance of the 19-gauge histology needle, along with the use of flow cytometry to enhance diagnostic yield where standard cytologic analyses have been negative [58], promises to change this. The diagnosis of lymphoma, using both cytology and histology needles, has been reported [20, 32, 59, 60]. Subcarinal needle biopsy has identified leiomyoma of the esophagus [21] and malignant pleural mesothelioma [61] while endobronchial aspirates have diagnosed both carcinoids [62, 63], and malignant melanoma [64].

Mediastinal masses have been diagnosed and therapeutically aspirated using the transbronchial route [65–69]. Hirano et al. [70] reported a sclerosing hemangioma, a relatively benign tumor, after a 21-gauge needle aspiration. Wang et al. [71] reported a patient with right paratracheal mass on CT scans consistent with a diagnosis of carcinoma. TBNA revealed serosanguinous fluid suggestive of a sterile abscess with no recurrence on later scans. In another report, decompression of a subcarinal cyst using TBNA allowed for safe anesthesia and the subsequent resection of the cyst [72].

Peripheral Nodules or Masses

TBNA of peripheral nodules and masses, using the cytology needle, has also emerged as an extremely useful technique in establishing a diagnosis. Most studies indicate that the yield from TBNA is higher than either from forceps biopsy alone or from a combination of conventional procedures. Tsuboi et al. [73] classified solitary pulmonary nodules (SPN) into four types according to the tumor-bronchus relationship: type 1: the bronchial lumen is patent up to the tumor; type 2: the bronchus is contained in the tumor mass; type 3: the bronchus is compressed and narrowed by the tumor, but the bronchial mucosa is intact, and type 4: the proximal tree is narrowed by peribronchial or submucosal spread of the tumor or by enlarged lymph nodes (fig. 5). TBNA is especially useful in increasing the diagnostic yield of flexible bronchoscopy in type 3 and 4 lesions in view of their submucosal/peribronchial location, making them relatively inaccessible to other diagnostic procedures performed through the FB, such as washing or brushing.

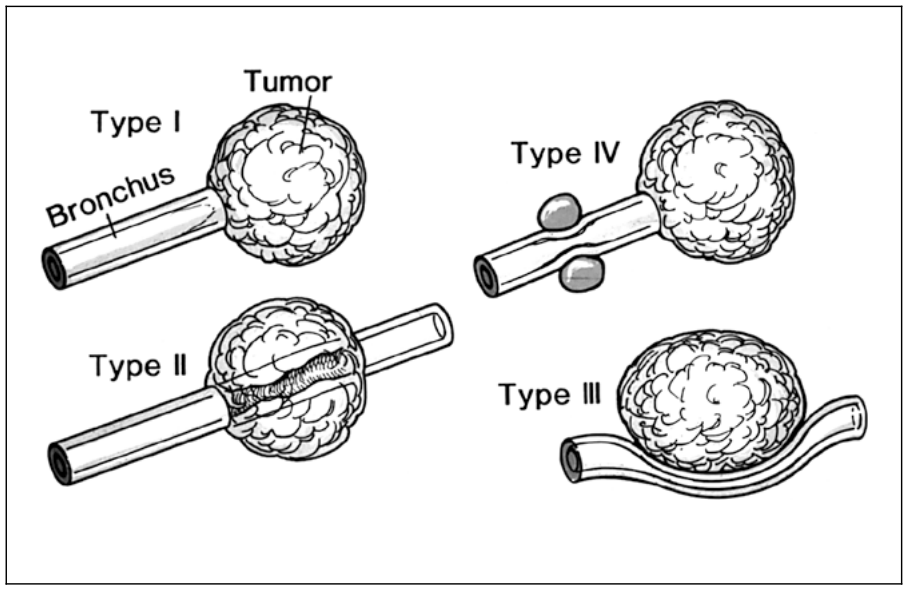

Fig. 5. Schematic representation of tumor-bronchial relationship. Modified from Tsuboi et al. [73].

Twenty-four to 30% of peripheral lesions can only be identified by TBNA (table 8). Lesion characteristics predicting increased diagnostic yield include: (1) lesion larger than 2 cm (76–83 vs. 33–58%), (2) concurrent mediastinal disease (89 vs. 46%) and (3) if the lesion is a hematogenous metastasis [7, 74–76, 78]. Although the yield from a combination of TBNA and forceps biopsy is lower than transthoracic needle aspiration (TTNA), it can be as high as 75%, thus eliminating the use of TTNA and its attendant complications [77]. TBNA should be the procedure of choice for all nodules and masses, except for a small subset of patients with lesions smaller than 2 cm, for whom TTNA may have a diagnostic advantage.

Table 8. Diagnostic yield of TBNA for peripheral nodules and masses as reported in the literature

Authors	n	TBNA+ n	TBNA+ %	TBNA exclusively
Wang et al. [74]	20	11	55	7*
Shure and Fedullo [7][1]	42	22	52	8*
Castella et al. [75][2]	45	31	69	12
Katis et al. [76][3]	37	23	62	8
Wang and Britt [79]	22	8	36	2
Gasparini et al. [77]	349	242	69	67
Wang et al. [78]	160	73	46	–

Reproduced with permission from Dasgupta et al. [22].
[1–3] Addition of TBNA increased diagnostic yield by 21, 27 and 24%.
* At least.

Airway Lesions

Endobronchial Lesions. The diagnostic yield of TBNA for visible endobronchial lesions has varied between 65 and 87% [9, 75, 80, 81], and has often been the only positive sample providing diagnosis [72]. Despite this, due to the reported high yield (67–100%) with forceps biopsy [38, 80–85] for visible endobronchial lesions, indications for TBNA are less clear. Clinical situations where TBNA of an endobronchial mass can be useful include: (1) when an endobronchial lesion is likely to bleed, such as a carcinoid, TBNA provides a safe method of obtaining a tissue diagnosis [62, 63]; (2) extensive crush artifacts on an endobronchial biopsy specimen have been reported in small-cell cancer (needle aspirations have been critical in establishing a diagnosis in these cases [86]); (3) a visible lesion with surface necrosis could lead to a negative forceps biopsy result (TBNA can help establish a diagnosis by obtaining samples from within the viable tumor mass).

Peribronchial and Submucosal Disease. The yield of conventional procedures such as forceps biopsy and brushing tends to be much lower in submucosal and peribronchial disease than for exophytic lesions for a variety of reasons: (1) peribronchial lesions are inaccessible to the

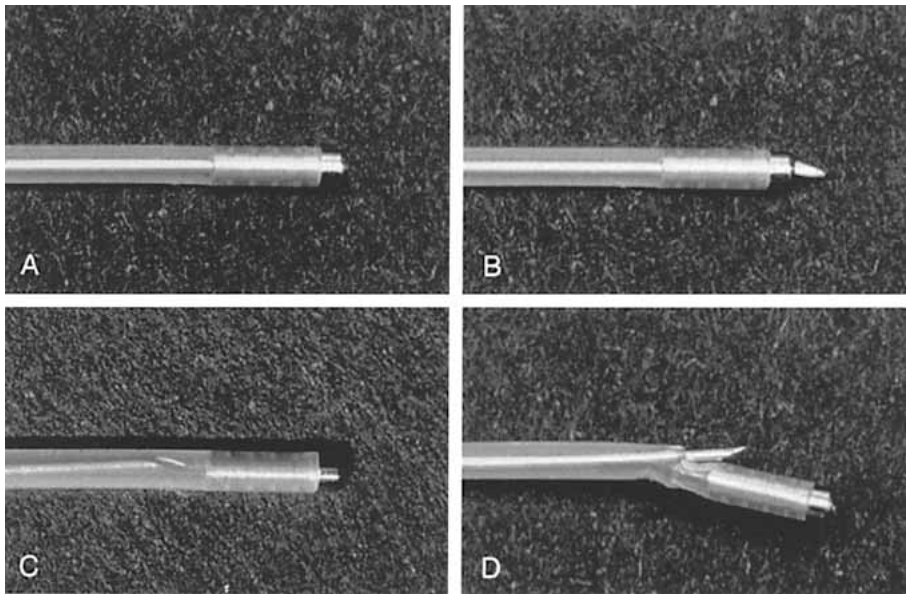

Fig. 6. A Correct position of the metal needle prior to TBNA: the entire beveled end is placed inside the metal hub. **B** Incorrect position of the metal needle: the sharp end of the needle is extending beyond the metal hub, which can potentially lacerate the working channel of the bronchoscope. **C**, **D** Incorrect position of the metal needle: the needle is placed too proximal to the metal hub and can perforate its own plastic catheter during forward thrust and potentially damage the working channel of the bronchoscope. Reproduced with permission [88].

biopsy forceps by virtue of being located outside the airway; (2) submucosal infiltration by tumor may make tissues firmer causing the forceps to slide off the lesion, and (3) the abnormal lesion may be covered by normal epithelium causing suboptimal sampling. Under such circumstances, addition of TBNA to obtain submucosal or peribronchial cytology samples could increase diagnostic yield [8, 9, 27]. Shure and Fedullo [8] studied 31 patients with submucosal and peribronchial disease; the sensitivity of biopsies obtained by forceps, TBNA, combination of both and combination of all conventional procedures with TBNA was 55, 71, 89 and 97%, respectively.

Complications

The most important complication following TBNA is related to damage to the working channel of the FB. This complication is related to the use of nonretractable needles as well as the 19-gauge needle [59, 87], and care needs to be taken while manipulating the catheter through the FB [23] (fig. 6). The incidence of fever and bacteremia has been debated, and there are no firm recommendations about antibiotic prophylaxis [89–91]. Transient bacteremia, 6 h after the procedure with prompt defervescence after antibiotic therapy has been reported. After TBNA of a subcarinal mass, 1 patient experienced a purulent pericarditis with polymicrobial mouth flora and required pericardiocentesis and catheter drainage [92].

Oozing of a minimal amount of blood from the puncture site may be encountered and usually represents dilated blood vessels in the tracheobronchial wall rather than invasion of a major vascular structure. Marked bleeding has not been reported even in anticoagulated patients [35, 60]. Although patients with superior vena cava obstruction have been felt by some to be at an increased risk of bleeding, a retrospective study of 15 patients encountered inconsequential bleeding in only 2 patients. The superior vena cava may actually be displaced anteriorly by enlarged paratracheal nodes, making inadvertent puncture less likely [93].

Rare complications include inadvertent liver biopsy in a patient with a raised right hemidiaphragm that did not lead to any adverse clinical consequences [94], 2 cases of pneumothorax and 1 each of pneumomediastinum and hemomediastinum [40, 77, 95, 96].

Conclusion

Despite its proven usefulness, TBNA remains underutilized. An American College of Chest Physician (ACCP) survey showed that only 11.8% of pulmonologists use TBNA [97]. Most pulmonologists in the 80s decade were not formally trained with TBNA during their fellowship program. This has unfortunately translated to minimal emphasis on TBNA in current programs in a large number of institutions [98]. Technical problems with the pro-

cedure (faulty site selection, incomplete needle penetration, catheter kinking preventing adequate suction), confusing array of needles, low yields, unproven concerns regarding safety of the procedure, inadequate cytopathology support and bronchoscopic damage have all perpetuated the limited utilization of this procedure. 'Hands on' experience with TBNA, familiarity and expertise with few needles only, careful attention to the anatomy, procedural technicalities and specimen acquisition may all help to increase the yield. Acquisition of skills with cytology needles should precede the use of the histology needle. Increasing education and experience can also increase diagnostic yields [39, 99]. Table 7 lists our recommendations for the routine use of TBNA in specific patient populations.

There remains no doubt about the diagnostic utility of TBNA. Formulating guidelines to ensure adequacy of TBNA exposure and training amongst existing pulmonary fellows needs to be implemented. Regional workshops, with hands on experience targeted to practicing pulmonologists organized under the auspices of the ACCP would go a long way to popularize the procedure. Initial low yields should not discourage or deter further use. Collaboration between thoracic surgeons, oncologists and pulmonary physicians is essential to set up a TBNA program within each institution. With time, it is expected that more and more pulmonologists would attain expertise with TBNA, and the full potential of this nonsurgical, cost-effective and safe procedure would be realized.

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Endobronchial Ultrasound of the Airways and the Mediastinum

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Summary

As all imaging procedures of the parabronchial and mediastinal structures have considerable limitations, we investigated the use of endobronchial ultrasound. Therefore, we adapted miniaturized 20-MHz probes to the special requirements inside the airways. After establishing a normal sonographic anatomy of the bronchial structures and the mediastinum, we investigated the feasibility of clinical application. Endobronchial ultrasound proved to be useful in high-resolution imaging of the multilayer structures of the bronchial wall and the adjacent mediastinal structures at a distance of up to 4 cm. In many instances, it was superior for staging of lung cancer and other pathologies. Lymph nodes could be easily localized for transbronchial/transtracheal needle biopsy, but tumor infiltration could not be predicted. Also, other pathologies such as vascular malformations, mediastinal masses, pathologies of neighboring organs and pulmonary lesions could be correctly diagnosed. Here, application of the probes via the esophagus also proved useful. Thus, we come to the conclusion that in the near future endobronchial ultrasound may play an important role in bronchology at feasible costs. Especially in on the spot decision making during diagnostic and interventional procedures it proved extremely useful. In ongoing prospective studies, we are currently investigating the place of this new technology in comparison to conventional imaging procedures.

The view of the endoscopist is limited to the lumen and the internal surface of the airways. Processes within the wall or on the outside in the vicinity of the airways can only be suspected from indirect signs such as discoloration and swelling of the mucosa, pathological vascularization, leveling of the cartilage relief, impression, displacement or destruction of the airway wall [1, 2]. Many pathologies of the airways include the parabronchial structures. As especially in malignancies this may be crucial for the fate of the patient, there is a need to expand the view beyond the confinement of the bronchial wall.

This is all the more true as recent radiological diagnostic procedures such as cat scan and MR have proved to be insufficient in mediastinal staging of lung cancer [3–5]. In a prospective study for evaluation of the TNM classification at our institution, we found preoperative clinical staging in only 60% congruent with postoperative staging. Especially, assessment of the mediastinal structures is comparatively poor [3]. Involvement of the lymph nodes by tumor is correctly diagnosed in only 50%; 25% are false positive (overstaged) and 25% false negative (understaged), which has also been confirmed by others [6]. As routine mediastinoscopy is negative in 60%, and 16% of those are also false negative, some authors advise transbronchial needle aspiration of the hilar and mediastinal lymph nodes to diagnose extensive mediastinal tumor infiltration and prevent unnecessary explorative thora-

cotomies [7, 8]. In conclusion, there is a need to improve the diagnostic procedures for these structures.

Endosonography has been proven to be superior to radiological imaging procedures and is well established in other fields of medicine [9]. This refers especially to gastrointestinal endoscopy, where it has its place in staging of carcinoma of the esophagus, cardia and colon-rectum and influences therapeutic decisions [10–16]. Thus, it has decisive influence on therapeutic decisions. For staging of mediastinal and parabronchial structures, external mediastinal ultrasonography is used in anterior mediastinal and subcarinal lesions, but is insufficient for staging of the inferior tracheal and the perihilar regions [17–19]. By transesophageal endosonography, the pretracheal, right and anterior left hilar structures are out of reach because of the interposition of the airways or lack of anatomical contact.

As the technical problems of endobronchial ultrasound are much more complex as compared to other organs, the technique could not be established for a long time. We have been investigating endobronchial ultrasound at our institution since 1989. Only after introducing significant technical improvements to devices that seemed suitable could we gain more extensive experience in clinical application. Some results have already been published in preliminary reports [20–23] and in an overview [24]. In this phase, besides development of suitable instruments, we were interested in establishing a sonoanatomy of the airways and mediastinal structures as well as the investigation of the clinical feasibility and its cost-effectiveness. Although the results have yet to be confirmed by prospective multicenter studies, endosonography of the airways at our institution is well established as diagnostic routine procedure besides conventional methods and frequently has considerable influence on therapeutic decisions.

Technical Considerations

In contrast to radiological exploration of the chest, where the imaging process depends mainly on the difference of absorption of the X-rays by water as compared to air, imaging by ultrasound depends on differences in transmission, absorption, scattering and reflection of ultrasonic waves by tissues of different impedance. The ultrasound waves are created by the so-called 'piezo-electric' effect. In a gramophone, mechanical vibrations of a crystal caused by sound waves are used to set off electrical signals that are retransformed to sound by the loudspeaker. If conversely, a crystal is connected to an electric alternating current, vibrations are exited. By its vibration, the crystal is emitting sound waves. The frequency of the waves corresponds to the frequency of the electric current. Frequencies beyond the hearing range of more than 20,000 Hz are defined as ultrasonic waves. In medical application, frequencies in the Mega Hz range are used for creating images. Ultrasound waves may be reflected if they hit an obstacle, which is used by the bat for orientation. The time from emission to reception of the signal depends on the distance to the obstacle. The intensity of the signal corresponds to impedance. In application for medical imaging, the crystal functions as sender and receiver, as during pauses between the signals it is emitting, it serves as receiver for the reflected sound waves. The reflected sound waves are transformed into electrical signals which are transported to an electronic ultrasound processor that transforms these signals into an image of different gray scales. Generally speaking, the intensity of the received waves is transformed into brightness (echogeneity), and the time elapsed from sending to reception is depicted as distance from the ultrasonic probe. Water has very low resistance and ultrasound waves travel with high speed, whereas air and bony structures are almost impenetrable and reflect the ultrasonographic waves almost completely. The processor is set to the speed of 1,540 m/s in average water containing tissue of 37 °C as standard for its calculation. Differences from this standard are shown as brightness or darkness. Thus, if a tissue contains a lot of water, the sound waves travel faster and it appears darker. The effect of deeper penetration through fluid is called enhancement. The opposite effect is complete reflection by impenetrable tissues which causes a shadow behind the obstacle.

Three major factors influence the quality of the ultrasonic image: contact of the ultrasonic probe with the tissue, depth of penetration of the ultrasonic wave and spatial resolution of the different structures. In order to enhance contact to surfaces, most of the probes are equipped with some kind of water cushion in front of the transducer. The lower the frequency of the ultrasonic wave, the higher the depth of penetration and vice versa; the higher the frequency, the higher the resolution of structures. These technical implementations have to be taken into account when applying ultrasound for diagnostic purposes and in interpretation of ultrasonic images.

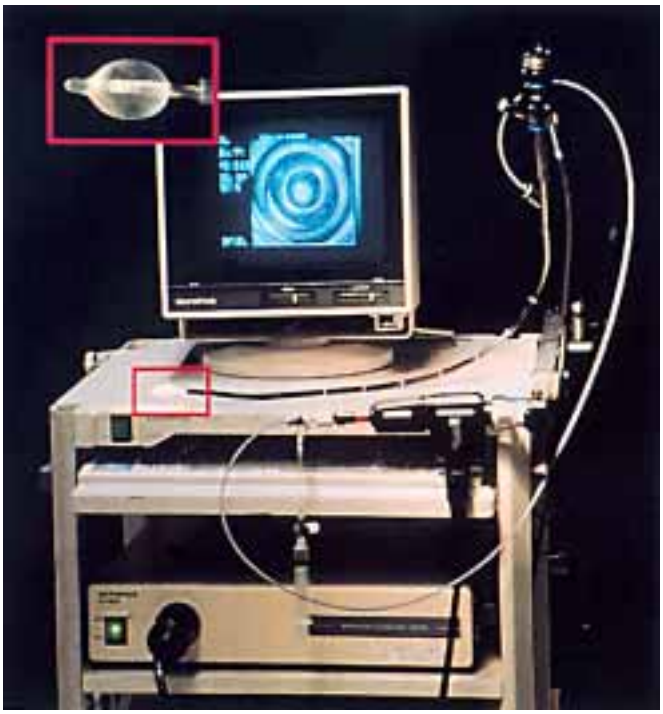


Fig. 1. First ultrasound system by Olympus Co. consisting of processor (EU-M 30), driving unit (MH-240), keyboard and monitor. The miniature probe (UM-3R) and balloon catheter (MH-246R) are introduced via the instrumentation channel of the fiberscope (prototype BF-ST 30), and the balloon is inflated by aqua dest.

Ultrasound Devices

Obviously, gastrointestinal sonoendoscopes could not be applied inside the airways due to their caliber. Therefore, some authors applied special ultrasonic bronchofiberscopes that have a curvilinear scanner with 7.5 MHz at one side of the tip [25, 26]. The maximum diameter of these devices is 6.3 mm. The image is very limited to a sectorial view of low resolution. For 360° imaging of the mediastinal structures, the instrument has to be rotated around its axis during the procedure, and the different planes have to be reconstructed like cat scan images. As by this procedure a direct coherent circular image of the mediastinal structures is impossible, we looked for a different solution by applying miniaturized probes that are used for endoscopic [27, 28] and cardiovascular endosonography [29, 30] with which we had gained preliminary experience in endovascular sonography of the pulmonary artery [31].

Among six systems tested in vitro, only two produced suitable images. Since 1990, we have mainly applied miniaturized Olympus probes of 7.5 MHz. Later, also probes of 12 and 20 MHz were available (UM-2R/3R, driving unit MH-240 and processor EU-M 20 and 30; fig. 1). The first probe had a diameter of 3 mm, and the mechanical single transducer at the tip was rotating at approx. 400 rpm and produced a 360° image perpendicular to its axis. Because of its large diameter, it was mainly applied during rigid bronchoscopy using a metallic tube as guide. Later, models of 12 and 20 MHz with a diameter of 2.5 mm could be introduced via biopsy channels of at least 2.8 mm with regular flexible fiberscopes.

The second system is the endovascular ultrasonic probe by CIVIS of Sonotron Company which had been tested by other authors, and with which we had already preliminary experience in ultrasonic investigation of the pulmonary artery. These probes have an outer diameter of 10 F (12 MHz) and 8 F (20 MHz). The axial resolution is 0.12 mm and the radial resolution 0.23 mm. Rotation of this mechanical transducer is 600 rpm. Therefore, it produces less motion artifacts than the early Olympus probes. The ultrasonic wave is reflected from the transducer by a mirror with an angulation of its surface of 30°. Thus, the ultrasonic image is slightly tilted forward from the tip of the ultrasonic probe.

We do not have any experience so far with the intracavitary scanner SSD-550 of Aloka Company which is sold for exploration of the gastrointestinal tract.

Technique of Endobronchial Ultrasound

The main problem of application inside the airways is coupling of the ultrasonic probe to the tracheobronchial wall. For this purpose, lobar and smaller peripheral bronchi can be completely filled with water or saline solution. This is impossible in the central airways. In these, with the naked probe, one gets only a very limited sectorial view. This is why we developed flexible introducer catheters for the Olympus probes that are equipped with a balloon at the tip (MH-246R). Once this balloon is filled with water, it completely fills the airway and provides a complete 360° view of the mediastinal structures. The water simultaneously serves as enhancing medium for the ultrasonic waves. Thus, under favorable conditions, the depth of penetration even for the 20 MHz waves may be up to 5 cm. This is why we now prefer these probes to the 7.5- and 12-MHz probes, because of their higher resolution. So far we were not able to equip the CVIS catheter with a similar device. Thus, their use is restricted to the peripheral airways and to the lung tissue.

Since the first balloon catheters had a diameter of 3.5 mm, they still could not be introduced through the biopsy channel of ordinary bronchoscopes. They had to be applied through rigid bronchoscopes, parallel to an ordinary flexible fiberscope or via a new flexible Olympus bronchofiberscope with an outer diameter of 7 mm (Olympus BF-ST 30). The biopsy channel of the latter instruments is large enough to allow the probe to be passed. The most recent probes (XUM-BS20-26R) now can be introduced through the biopsy channels of routine fiberscopes together with the balloon sheath (XMAJ-643R).

Once the probe is placed inside the airways under visual control, the balloon is filled until close contact to the wall is established (fig. 2). This can be achieved without any problems up to the main bronchi as long as both lungs are ventilated. If one main bronchus is occluded after contralateral pneumonectomy or during investigation of the trachea, complete occlusion of the airway under local anesthesia can even be shortly tolerated under sufficient sedation and after careful preoxygenation (preferably via an orotracheal tube). General anesthesia allows up to 3 or 4 min of apnea for investigation of the mediastinal structures [32]. According to our opinion even this procedure is justified with respect to the useful additional information that can be obtained.

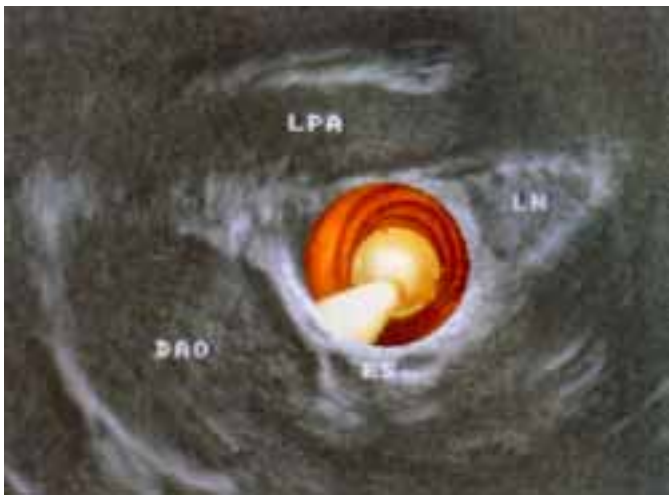


Fig. 2. The balloon is filled with water and gains complete circular contact while the transducer rotates inside. In this way, a circular image of the parabronchial structures can be produced. On the composed image, the structures surrounding the left main bronchus can be seen: the descending aorta (DAO), left pulmonary artery (LPA), esophagus (ES) and an enlarged lymph node (LN).

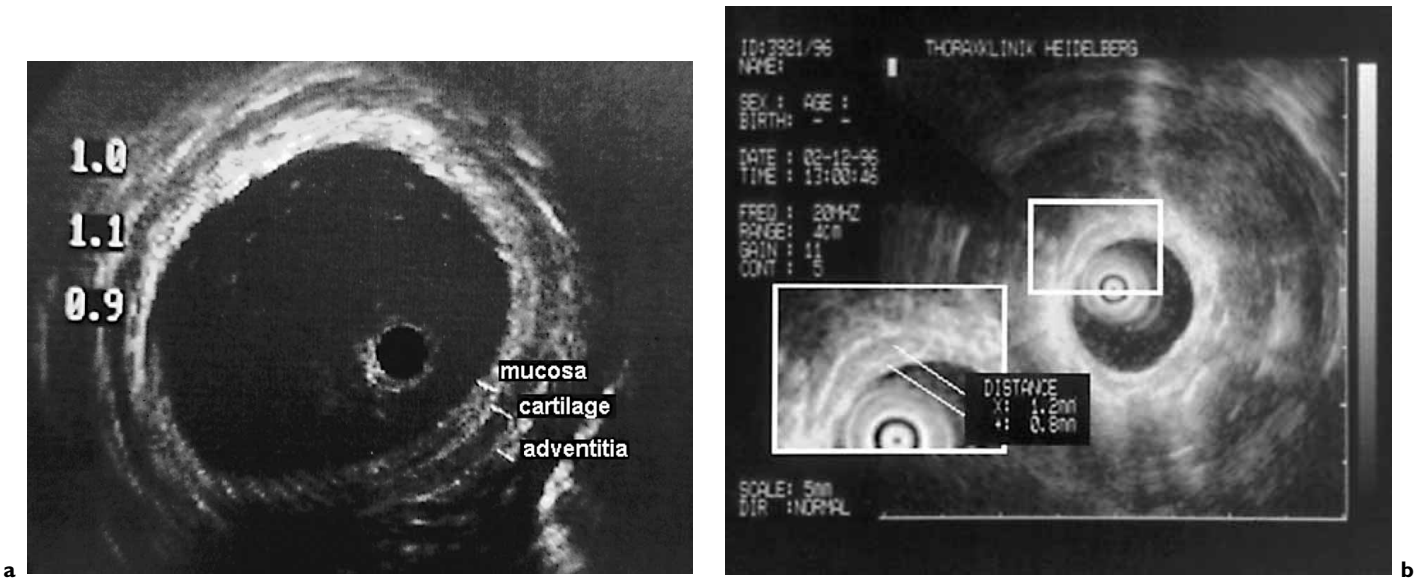
Imaging Artifacts

In an in vitro model, the Olympus probe and the CVIS probe provided exact measurements of distances perpendicular to the axis of the source. But because of their slower rotation Olympus probes were less reliable in calculation of distances on different perimeters around the probe [33]. In addition they showed considerable motion artifacts. This has been improved in the more recent devices. Due to the slower imaging process, displacements of the probe by pulsation and respiration causes artifacts. But as these artifacts are not synchronous with the physiological movements, they are easily recognized, and after some time of accommodation they no longer interfere with the diagnostic process.

As is known from other applications, multiple reflections, comet-like extension of reflexes and mirror reflexes may occur. The most frequent artifact are multiple repeated echoes resulting from reflections at the inner surface of the balloon that may vary with the material. Obviously, not all types of latex are equally penetrable for the ultrasonic wave. This is why we were not able so far to find a suitable material for the CVIS catheter. As the central airways are surrounded by strongly reflecting structures like lung tissue, vertebral column, calcified cartilages or lymph nodes, artifacts may also occur due to these strong reflections. Frequently, lymph nodes may show distorted triangular contours at the far side and depending on their echogeneity, the distal contours may be blurred.

Sonographic Anatomy

By in vitro studies of animal and human specimens, we could observe a complex seven-layer sonographic structure of the central airways in opposition to the description of some other authors. Probably due to application of probes with lower frequencies, they only recognized three layers [27, 28]. The mucosa on the inner surface shows a very bright echo that is further enhanced by the adjacent balloon. The submucosa is comparatively echo poor and clearly distinguishes the mucosa from the supporting structures of the tracheobronchial wall. The internal structures of the cartilage itself and of the intercartilagenous connective tissue are equally echo poor and cannot be differentiated from each other. But the strong echo of the endochondrium and of the perichondrium can always



a b

Fig. 3. Sonoanatomy of the tracheobronchial wall in vitro (**a**), showing the seven layers of: mucosa/submucosa, cartilage and adventitia (thickness in mm), and in vivo where usually they can only be recognized by higher magnification (**b**).

be seen in the intact structure. The adjacent external sonographic double layer structure of the supporting connective tissue and of the adventitia are easily missed under low power magnification due to the bright reflex of the perichondrium. Differentiation of these structures is important for the diagnosis of destruction by inflammatory processes or by submucosal and intramural malignant infiltration (fig. 3a, b).

Orientation within the mediastinum is difficult [34]. Besides the complex anatomy of the mediastinal structures and motion artifacts by respiration and pulsation, this is mainly due to the frequently unusual plains of the sonographic image as we have to follow the path of the airways. Inside the trachea, the ultrasonic image equals the horizontal plane we are used to in CT scan of the mediastinum. Passing into the main bronchi, the image continuously tilts towards a more sagittal plane, especially as we enter the left main bronchus. Passing into the peripheral part of the upper lobe bronchi, we even get an inverse horizontal plane.

During clinical use, recognition of distinct anatomical structures and their relationship usually is more helpful than localization of the probe itself (fig. 2). The vessels are easily recognized by their low internal echo and by their pulsation. But even after application of echo contrast medium, differentiation of arteries and veins may be difficult due to a lot of anatomical variations. By generally using pulse-oxymetry, arteries may be recognized because of their synchronous pulsation. Lymph nodes, in contrast, are more echo dense and can be detected down to a size of a few millimeters.

As the depth of penetration may extend up to several centimeters, the left atrium and even the mitral valve may be visualized from the distal left main bronchus. Closer to the bifurcation, the pulmonary trunk and left and right main pulmonary arteries can be seen ventrally to the left main bronchus, as well as the ascending aorta and the aortic arch. The descending aorta, the oval-shaped multilayer structure of the esophagus and the vertebral column are distinct landmarks for orientation. The small but important area between left pulmonary artery and aortic arch – the so-called aortopulmonary window – can be visualized from the roof of the left main bronchus. Sometimes, in addition, passage to the apical segmental bronchus of the left upper lobe proves to be helpful.

Ventrally to the right main bronchus, the pulmonary trunk, the aortic root and the vena cava are seen as well as the right pulmonary artery. Closer to the bifurcation, dorsally, the esophagus is found and laterally, to the right side, the vena azygos, which crosses at the level of the right tracheobronchial angle, ventrally of which its junction with the vena cava can be seen.

From the lower trachea, in addition, the aortic arch and some of its branches, as well as the pulmonary arteri-

Table 1. Indications of endobronchial ultrasound 1994–6/1996 (1,020 procedures in 869 patients)

	%	n
Endobronchial carcinoma		
Intraluminal extent	19	193
Penetration	2	24
Early cancer?	3	26
Posttherapy control	3	27
Mediastinal infiltration		
Trachea	6	61
Pulmonary artery	3	33
Large vessels	3	30
Esophagus	(sep. table)	
Lymph nodes (incl. guided biopsy)	29	299
DD carcinoma/benign lesion	18	183
Intramural lesion	4	43
Mediastinal tumor		
Malignancy	2	22
Others	2	23
Perioperative control (anastomosis/recurrence)	5	51
Other	1	5
Total	100	1,020

DD = Differential diagnosis.

Table 2. Indications of endoesophageal ultrasound 1994–6/1996 (188 procedures)

	%	n
Primary cancer	6	11
Control therapy	4	8
Benign intramural lesion	3	6
Infiltrating lung cancer	15	28
Mediastinal extension	6	12
Infiltration of large vessels	2	4
Mediastinal lymph node	28	52
Exclusion of tumor	24	45
Mediastinal tumor	4	7
Benign process	7	14
Control of anastomosis	1	1
Total	100	188

Table 3. Endobronchial ultrasound in interventional bronchoscopy 1994–6/1996 (210 procedures)

	%	n
Mechanical desobliteration	28	58
Stent implantation	16	34
Laser resection	12	25
Brachytherapy	11	24
PDT	2	5
Guided biopsy	8	16
Abscess drain	11	23
Mucoid impaction	7	14
Perforations/fibrin	5	11
Total	100	210

PDT = Photodynamic therapy.

al trunk, are easily seen. Pathological structures of soft tissue or cystic appearance are clearly differentiated from these organs by their different echo structure.

Inside the peripheral bronchi, conditions for echography are not so favorable, as the surrounding air-containing structures reflect the ultrasonic waves. In some instances, solid structures or cystic formations can be differentiated within the lung parenchyma, which may be helpful in guiding diagnostic and bioptic procedures [35].

Results of Clinical Application

Already during the first phase of our investigations in developing the sonographic system, we gained enough experience in clinical application to give first preliminary reports [2, 20, 21]. In a first nonprospective feasibility study, we investigated whether by use of the new optimized system we were able to gain additional information that we could not obtain by other conventional methods. In addition, we analyzed cost-effectiveness by resterilizing and reusing the originally single-use vascular transducers until they broke [36]. With the system of Olympus Company, we performed more than 1,600 examinations. In a preliminary retrospective study, 1,418 of these, performed during the period from June 1994 to December 1996 in 869 patients, have been analyzed; 1,020 examinations were performed in the tracheobronchial system (table 1), 188 in the esophagus (table 2). In 210 cases, endosonography was applied for interventional procedures (table 3). The different indications may be drawn from the tables.

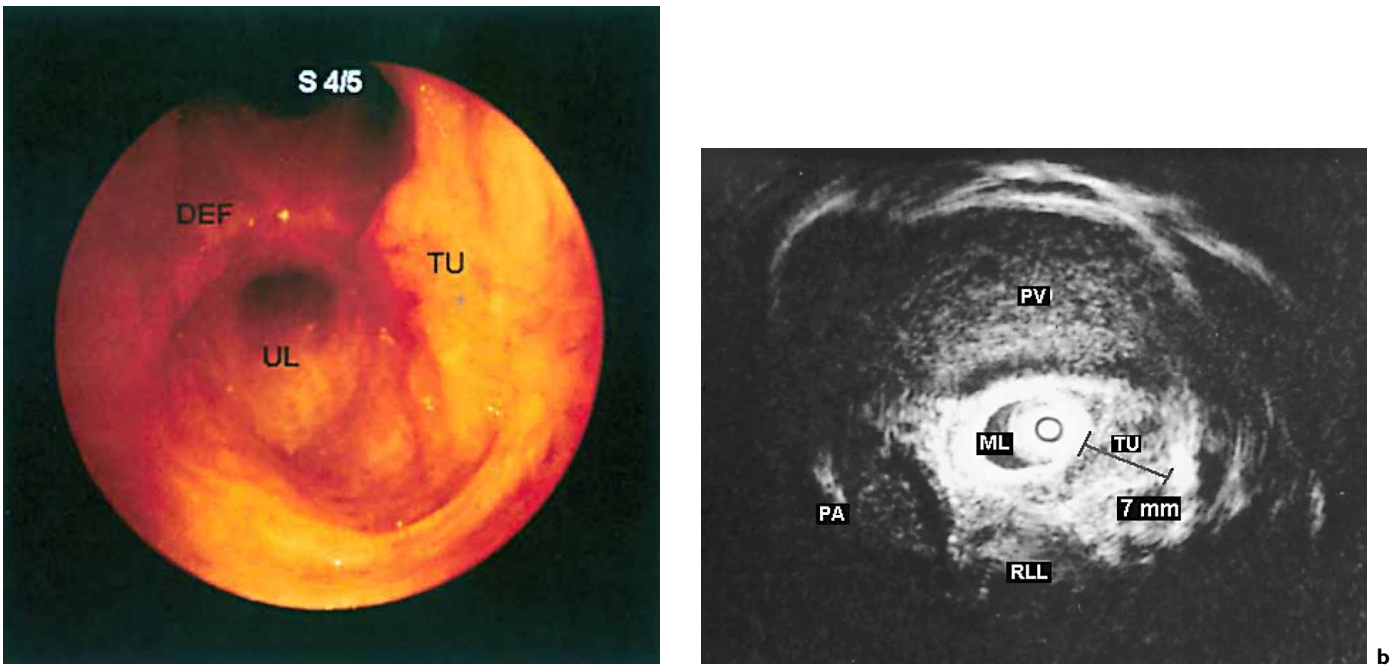


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Fig. 4. Early cancer in the middle lobe. Laterally to the middle lobe ostium, a small protrusion of the bronchial wall may be recognized which represents a small squamous cell carcinoma. The slightly bleeding defect on the carina to the middle lobe (S 4/5), ventrally to the lower lobe ostium, resulted from biopsy (DEF) (**a**). The tumor was neither visible on plain X-ray nor on CT scan, which is a common definition for early lung cancer. Ultrasound examination of the middle lobe bronchus (ML) demonstrates a lesion of 7 mm (TU) in diameter which is confined to the bronchial wall. Pulmonary artery (PA) and vein (PV) are intact (**b**). The patient was treated by lower bilobectomy. UL/RLL = Right lower lobe.

Staging of Bronchial Carcinoma

The goal of staging is the exact diagnosis of the TNM formula as base for rational therapy. The different criteria for extent of tumor growth are defined by the latest TNM classification according to UICC and the supplement of 1997 [37]. For the bronchoscopist, this means in small radiologically invisible tumors detection and localization of early carcinoma in the case of positive sputum cytology. Therapeutic decisions in these cases are made on the basis of endobronchial extension, infiltration of the tracheobronchial wall and last but not least on the pathoanatomical diagnosis. For the assessment of infiltration of the hilar and mediastinal lymph nodes, exact localization is necessary prior to transbronchial and transtracheal needle biopsy [38]. Defining size according to longitudinal and cross diameter, analysis of the internal structure and relation to the central airways and the mediastinal structures are important features that are analyzed by endosonography. Some types of metastasis localized within the mediastinum, in the central airways, inside the lung or the pleura can be within reach of the bronchoscopist. Especially in regions which are not accessible to the direct view of the endoscopist, we expected additional information by endobronchial ultrasound.

Primary Tumor

Early Carcinoma. Frequently, tumors that are not visible by high-resolution CT scan are defined as early carcinoma. This is not in accordance with our experience. The usual pathoanatomical definition of early cancer is lack of infiltration beyond the submucosa. According to our experience and other studies, it is well known that only 75% of tumors that are visible by bronchoscopy are detected by radiology [6]. Among those not detected, there are many tumors with extensive local infiltration. In several patients sent for endobronchial treatment of so-called early bronchial carcinoma, we could demonstrate deep infiltration of the bronchial wall and sometimes even regional lymph node metastasis which had escaped all other meth-

ods of diagnosis. This is why we believe that the diagnosis of early bronchial carcinoma can only be established from the resection specimen by the pathologist. By clinical methods, we can only assume the depth of infiltration.

In every case of macroscopic alteration of the mucosa, we found concomitant alterations in the sonographic structure. The wall was more or less thickened and the delicate structures no longer visible. The altered sonographic structure was very variable, ranging from very low to very high echodensity [16]. In many instances, even if the mucosa seemed to be intact macroscopically, we found submucosal tumor spreading by endobronchial ultrasound. In some instances, it could be followed extending beyond the bronchial wall into the parabronchial structures. If we do not see any signs of infiltration of the deeper layers of the tracheobronchial wall or the adjacent lymph nodes, this strongly suggests a localized tumor which may be treated endoscopically with curative intent if the patient is considered to be inoperable for local or general reasons (fig. 4a, b) [36, 39].

Intraluminal Extension and Involvement of the Tracheobronchial Wall. Also in advanced bronchial carcinoma, endoluminal ultrasound provides valuable information for therapeutic decisions. In complete airway obstruction, we were able to differentiate the basis and the surface of the tumor, and we could assess depth of invasion into the bronchial wall and into the mediastinum. By passing the stenosis, we could assess patency of the distal airways (fig. 5a–f). This information was of importance for endobronchial desobliteration, especially if we could prove simultaneously that the pulmonary artery was not occluded [39]. In occlusion of a central airway, perfusion of one lung may be completely shut down due to the Liljestrand-Euler reflex. In this case, perfusion scan is unable to prove organic occlusion of the pulmonary artery, and usually pulmonary angiography has to be performed, because bronchial recanalization in cases of complete occlusion of the pulmonary artery would only increase dead space ventilation. In some patients, on the other hand, we could demonstrate direct invasion of the pulmonary artery or complete occlusion which could be confirmed by angiography or postoperative pathological examination.

Infiltration of Mediastinal Structures. Even more important in preoperative staging is the diagnosis of infiltration of the organs in the mediastinum such as the aorta, vena cava or the main pulmonary artery which by radiological methods frequently proves to be difficult. Tumors of the left hilum are situated in close vicinity to the esophagus, and in several instances, we could demonstrate direct infiltration of the esophageal wall by echography of the left main bronchus or the distal trachea. If either of these organs is infiltrated by a tumor, surgery is no longer possible (fig. 6a–c). If we can demonstrate a clear sonographic demarcation of the tumor to these structures, and if signs of infiltration of the wall are missing, we can assume that the patient will be operable. This could be repeatedly confirmed by the intraoperative situs. Intratracheal ultrasound was especially helpful in diagnosing external infiltration of the tracheal wall by tumors of the mediastinal surface of the lung or by primary mediastinal tumors. Here, in our experience, endobronchial ultrasound proved to be superior to radiological examination.

Involvement of Lymph Nodes

Therapeutic decisions in bronchial carcinoma are even more dependent on lymph node involvement than on extension of the primary tumor. This is why exact staging of lymph nodes is extremely important. Under favorable conditions, we could visualize lymph nodes down to a size of 2–3 mm, and we were able to recognize the internal delicate architecture of lymph follicles and sinuses as well as small lymph vessels of the hilum. But in opposition to other localizations, for example in ENT tumors [40, 41], we were not able to find reliable signs for diagnosis of malignant infiltration. In a limited prospective in vitro study, we therefore examined 84 lymph nodes of 15 patients which had been surgically resected for the treatment of bronchial carcinoma. But even under these favorable conditions, we could find no reliable criteria for the malignant infiltration, neither with regard to the echogeneity nor to homogeneity of the internal structure or with respect to boundary to the surrounding structures, although the resolution was below 1 mm. We assume that this is due to the high rate of unspecific alterations, such as inflammatory reactions in postobstructive pneumonia, silicotic or specific scar formation and other pathological reactions which cause alterations in the internal structure. As the importance of transbronchial/transtracheal needle aspiration has been proven for staging of regional lymph nodes [7, 8, 38] the addition of endobronchial ultrasound for improvement of these procedures has been investigated. Preliminary results showed that prior or simultaneous ultrasonography may reduce the number of attempts and improve results [42]. As by the Olympus system simultaneous control of the biopsy needle is very limited, echography mainly serves for localization of the lymph nodes (fig. 7). Transbronchial/transtracheal needle

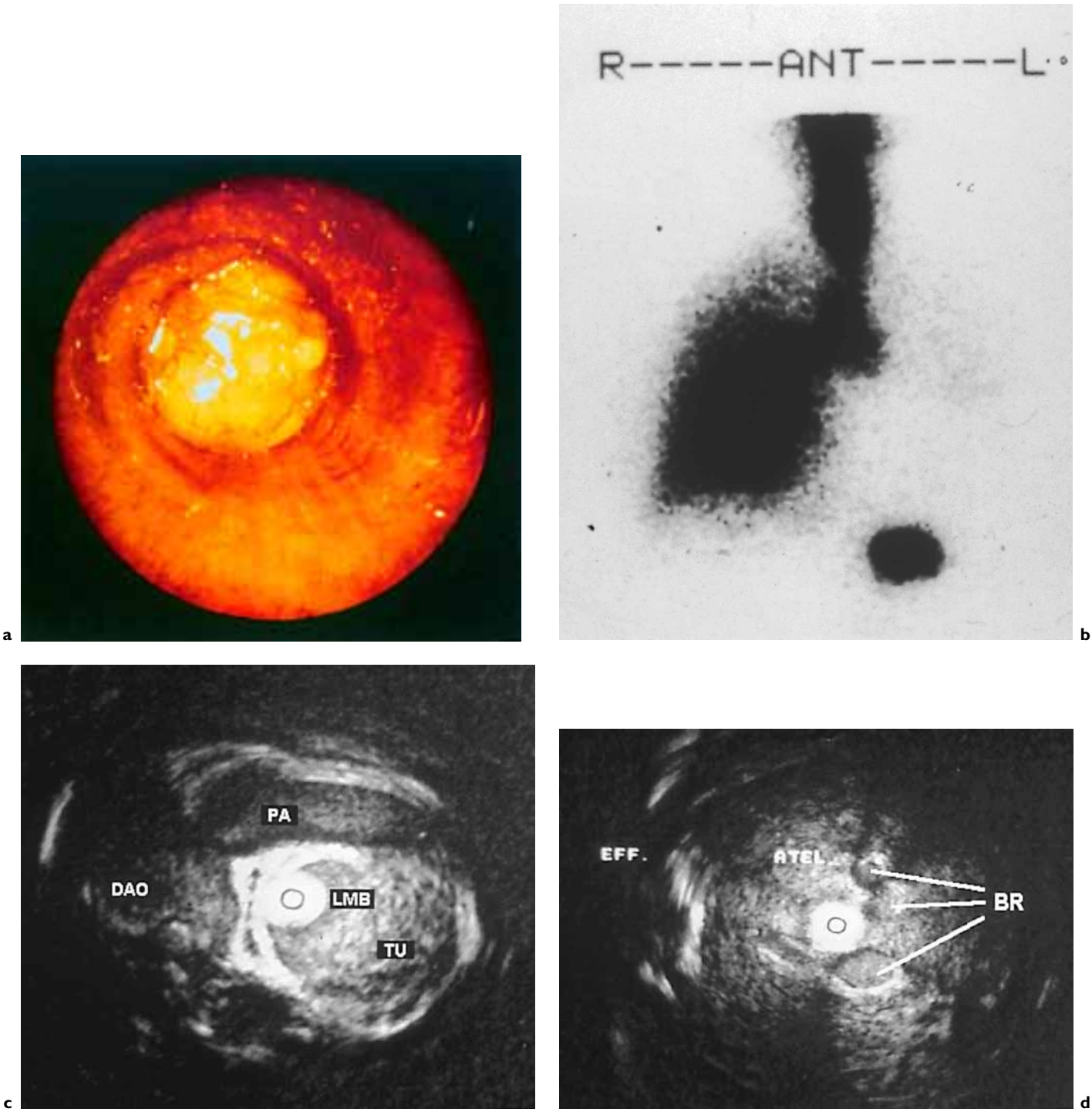
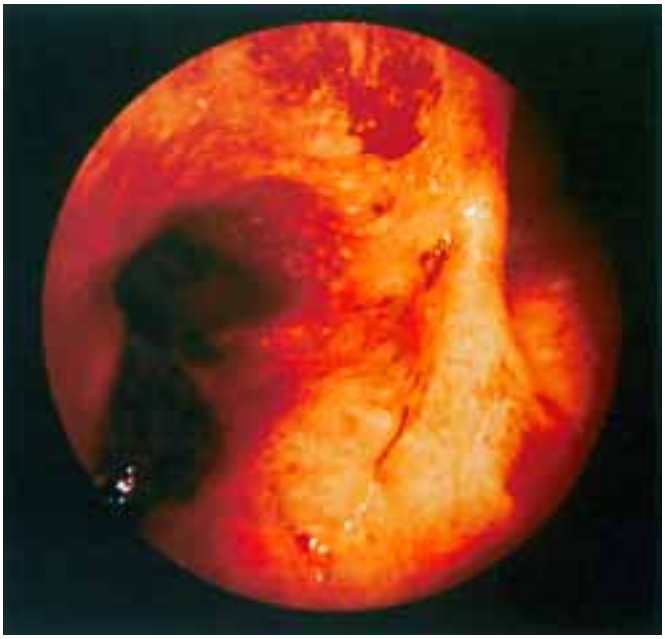


Fig. 5. a Complete obstruction of the left main bronchus by exophytic bronchial carcinoma. **b** Perfusion and ventilation scan demonstrate complete loss of function of the left lung. **c** Endosonography shows the base of the tumor (TU) to the right at the mediodorsal wall (LMB). The lateral and ventral wall is intact. The left pulmonary artery (PA) is patent, but shows a smaller caliber due to reflectory reduction of perfusion (Euler-Lijestrand mechanism). Also the descending aorta (DAO) is unharmed. **d** Beyond the tumor, the bronchi of the lower lobe (BR) are filled by secretions but patent. The lung is atelectatic (ATEL) and some pleural fluid is seen (EFF). **e** After laser resection, the main bronchus is opened. **f** Ventilation of the lung is restored.



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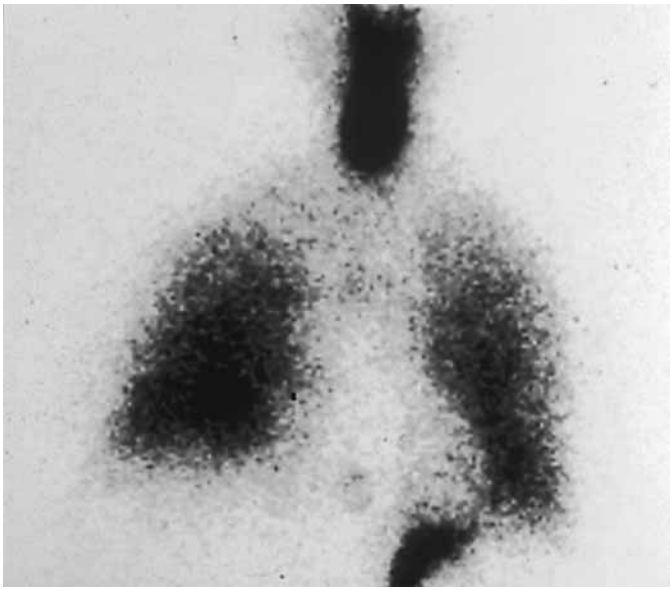

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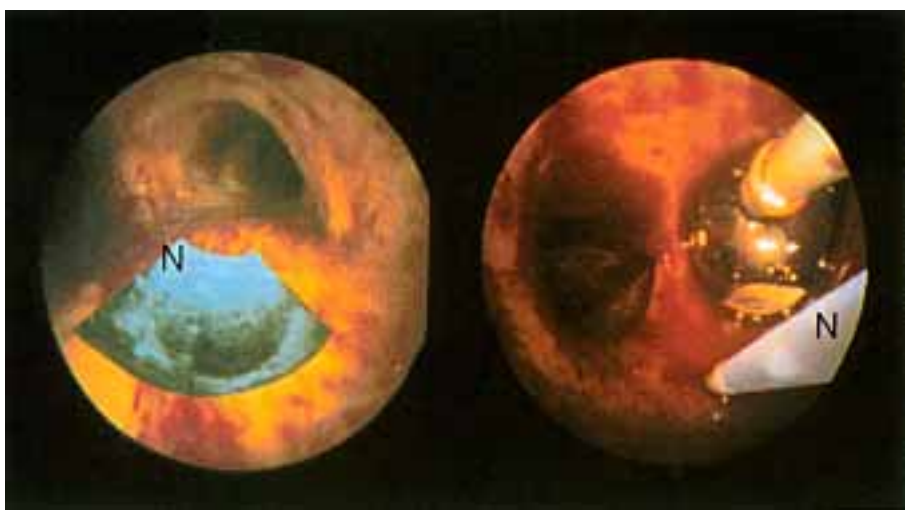


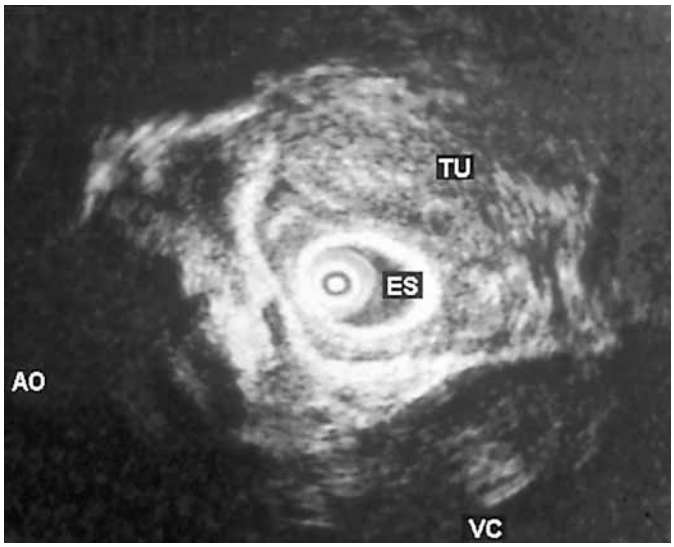
Fig. 6. An enlarged lymph node is localized by endobronchial ultrasonography dorsally to the bifurcation (**a**) and in this case, a needle (N) is inserted into the node parallel to the ultrasonic probe (**b**). It can be clearly seen as a bright dot with a dorsal shadow within the lymph node (**b**).

biopsy is performed sequentially after prior sonographic localization. This is easy as the cartilages and branches allow exact anatomical localization and guidance of the biopsy needle. In larger malignant lymph nodes, in which invasion of the bronchial wall can be sonographically proven, so-called 'button-hole' biopsies can be performed by removing the mucosa and taking biopsies of the deeper layers of the bronchial wall without the risk of inducing pneumothorax or pneumomediastinum.

Mediastinal Masses

Mediastinal masses can only be visualized by endobronchial ultrasound and subsequently approached by transbronchial/transtracheal needle biopsy if they are localized in close contact to the central airways or if some fluid-containing structure provides an acoustic window. Retrosternal masses or those which are localized in far distance within the dorsal mediastinum cannot be approached in this way due to lack of penetration of the

a



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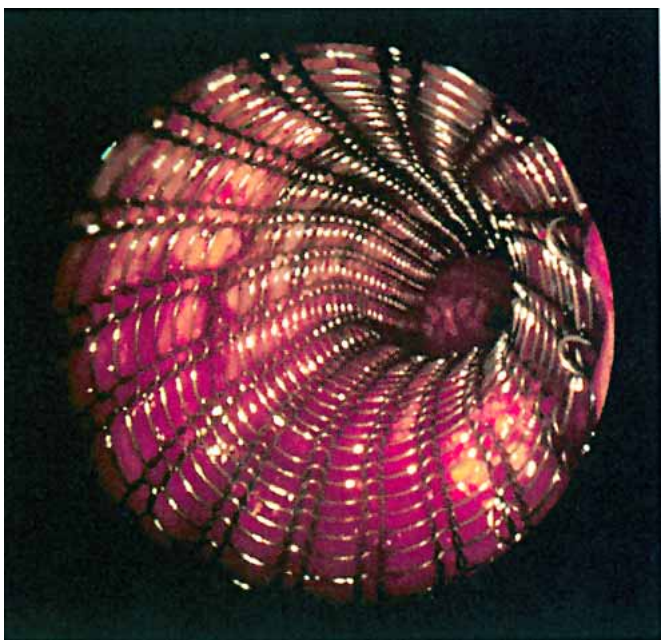

c

Fig. 7. Bronchoscopic desobliteration of obstructing tracheal tumor. Bronchoscopy shows an exophytic tumor of the lower trachea with almost complete obstruction. After emergency treatment by Nd:YAG laser, coagulation and partial resection (**a**), the extent is explored by endoesophageal ultrasound for suspicion of infiltration of the esophagus (**b**). Although endoscopically the esophageal mucosa seemed completely intact besides compression, endoluminal ultrasound reveals extensive tumor infiltration (TU) which can be diagnosed from the extinction of the layers of the ventral wall as compared to the intact dorsal wall. AO = Aorta; VC = vertebral column; ES = esophagus. Surgery in this situation is out of question and additional radiotherapy after complete laser resection bears a high risk for esophagotracheal fistula. Therefore, after partial resection, a Nitinol Ultraflex stent is implanted to keep the lumen patent during radiotherapy (**c**).

ultrasound through the surrounding tissue. Primary mediastinal or bronchogenic cysts are easily differentiated from solid tumors by their echo-poor internal structure which is frequently septated, provided that they are in close contact to the airways. In solid masses, according to our experience, endosonography is superior to radiological procedures in differentiation of compression and infiltration of the wall of the airways. This applies for example to goitre and thyroid carcinoma. In tumors of the mediastinum, which are usually localized ventrally to the trachea and the left main bronchus, access via the apical segment of the left upper lobe is preferable due to its close relation. Sometimes tumors of adjacent mediastinal organs, such as leiomyomas of the esophagus, can be diagnosed from the left main bronchus according to the typical extension between the different layers of the esophageal wall.

Large Intrathoracic Vessels

The large intrathoracic vessels adjacent to the central airways can be recognized easily due to their low echo structure and their pulsation. Due to a lot of variations, differentiation between arteries and veins can be difficult, even with additional application of echo-contrast media. The importance of sonographic diagnosis in direct tumor invasion has been mentioned. Especially in early infancy and childhood, compression of the airways by vascular anomalies is comparatively frequent. We repeatedly detected such anomalies by endobronchial sonography, even if extensive previous cardiovascular diagnostic procedures did not show the pathology. This is why we are convinced that in the future endosonography will be a standard procedure in the diagnosis of pediatric malformations. This applies also to extensive thoracic deformities where compression of the airways by deviation of the heart, the large intrathoracic blood vessels and the thoracic wall can be diagnosed easily by endobronchial ultrasound preventing more invasive radiological procedures like angiography. This, in our experience, was also true for compression due to aortic aneurysms or for internal displacement after extensive surgical procedures. In one case, we were even able to diagnose the rupture of a vascular flap for treatment of an aortic isthmic stenosis and the resulting aneurysm as cause for severe hemoptysis from the left upper lobe. The diagnosis was confirmed by surgical revision. Diagnosis of pulmonary embolism via the endobronchial route is a rare event, as suspicion of pulmonary embolism is no indication for an invasive procedure like bronchoscopy. If considered necessary after all, diagnosis is achieved more easily via the transesophageal route. This is also true for thrombosis of the pulmonary vein which we were able to diagnose in rare cases of severe postoperative hypoxemia, as the left atrium and the pulmonary veins are easily visible from the esophagus or from the left main bronchus.

Intrapulmonary Lesions

According to our experience, endobronchial ultrasound will not play a major role in diagnosis of intrapulmonary lesions as it is almost completely reflected by the surrounding air, and radiological imaging here is far superior [27, 28]. Only in some cases of atelectasis were we able to gain further information by endosonography in differentiation of bronchial obstruction by lymph nodes or tumors from compression by pleural fluids or masses. Some authors reported that endobronchial ultrasound may be helpful in guiding the biopsy needle in puncture of peripheral coin lesions. One group described an ultrasonic probe with integrated biopsy channel [35]. In some cases, we were able to explore intrapulmonary cavities by the ultrasonic probe and demonstrate internal fungus balls or tumors in the wall. In these cases, endobronchial ultrasound might be helpful in directing interventional maneuvers like the insertion of pigtail catheters for drainage of intrapulmonary abscesses.

Pleural Space and the Neighboring Organs

If an atelectasis or pleural effusion provides an acoustic window, the pleural surface and mediastinal structures may be visualized. Thus, we were able to see solid formations of the visceral and mediastinal pleura or on the pericardium. Diagnosis of organs localized in the direct vicinity of the airways such as the thyroid and the heart have been mentioned. Endobronchial ultrasound proved to be extremely valuable in diagnosis of infiltration of the esophagus by bronchogenic carcinoma. In this case, surgical procedures usually are no longer indicated. Also endobronchial procedures like ND:Yag laser therapy in combination with high-dose endoluminal radiation bear a high risk of fistulas. In these cases, prior assessment of the local situation by additional transesophageal exploration is extremely helpful.

Transesophageal Exploration

In addition to endobronchial application, we explored the application of the miniaturized probes in the esophagus. The images we obtained were equal to those generated by ultrasonic endoscopes [29]. The depth of penetration for the 20 MHz probes is obviously limited. This, however, was not so important since our major interest was assessment of infiltration of the esophageal wall by bronchial carcinoma or that of the airways by esophageal carcinoma (fig. 7a–c). Also, benign intramural processes such as leiomyomas and intramural diverticulosis could be clearly diagnosed and differentiated from malignant processes. Sometimes enlarged lymph nodes of the aortopulmonary window are detected more easily via the esophageal route. This is also true for the left atrium and the pulmonary vein. Detailed analysis of the chambers of the heart and its valves, however, is not possible because of the limited range of the 20 MHz probe.

Some indications for the use of endobronchial ultrasound in making therapeutic decisions have been mentioned before. This was the case in 20% of our examinations (table 3). For example, in exploration of central airway stenosis, sonography was useful in assessment of its extension and cause in order to choose the best method for interventional procedures, i.e. dilatation, laser or stent implantation as well as control of the therapeutic effect (fig. 6a–c).

Especially in bronchoscopic treatment of malignant tumors with curative intent such as photodynamic therapy and endoluminal high-dose radiation, it is important that the lesion is restricted to the bronchial wall. Here, endobronchial sonography proved superior to all other diagnostic procedures.

Correct endoscopic judgement of the healing process of an anastomosis after a so-called bronchoplastic surgical procedures (sleeve resection) can be problematic. Thus, it is sometimes difficult to differentiate superficial necrosis with mucosal swelling and fibrin deposition from imminent dehiscence. Endobronchial ultrasound proved to be very useful in assessment of the surrounding structures. In some cases, beginning perifocal abscess adjacent to the pulmonary artery was diagnosed by ultrasound before the onset of hemoptysis, and thus a timely decision for surgical intervention could be made.

Cost-Effectiveness

By reusing the ultrasonic probes repeatedly after resterilization and carefully avoiding too much pressure against the bronchial wall which causes fracture of the wire, with the CVIS probe we could examine 40–50 consecutive patients before mechanical defects occurred. Calculating the price of USD 750 for one catheter, the single procedure comes to about USD 15–20 in addition to the costs of the bronchoscopy, the investment of the processor of about USD 100,000 not included. The probes of Olympus company are somewhat more expensive, but they are much more resistant, so that we could use them a few hundred times. In conclusion, we consider the endoluminal ultrasound as a cost-effective and very rewarding additional diagnostic procedure.

Conclusion and Future Aspects

In conclusion, with regard to the technique, the clinical application and its diagnostic results, and the cost-effectiveness of endobronchial ultrasonography in addition to conventional diagnostic procedures, in our institution, endobronchial ultrasound already at this stage proved to be of the same value as in other disciplines, where it is already a routine procedure. In a currently ongoing prospective multicenter study, we intend to establish sound indication for endobronchial ultrasonography as compared to conventional methods of ultrasound, radiological and other diagnostic procedures. In addition, we intend to develop further technical improvements for the endobronchial application. This could include addition of Doppler sonography for analysis of vascularization, which could be helpful for example in the control of bronchial anastomosis after surgical procedures. Further, computerized analysis of tissue characteristics could be useful for the detection of malignancy of early carcinoma or lymph node metastases [43–45].

Addition of a biopsy channel would enable simultaneous sonographically guided needle biopsy [35], and first integrated systems are in planning. Since the results of treatment of advanced bronchial carcinoma have been disappointing so far, detection and treatment at early stages have gained new interest. Especially new methods like automated sputum cytology analysis in persons at risk and localization of radiologically and macroscopically invisible early carcinoma by fluorescence methods will be used more widely. In this concept, endobronchial ultrasonography is an ideal instrument for assessment of local extension and involvement of lymph nodes for staging before the decision for curative treatment by bronchoscopic means is made [36, 39]. We therefore strongly believe that endobronchial ultrasound will be a routine procedure in the future and play an important role in diagnostic and interventional bronchoscopy.

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Foreign Body Removal in Adults and Children

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Summary

Foreign body aspiration (FBA) is a common problem in small children and may result in potentially life-threatening complications. Although the clinical picture is usually highly suggestive, almost one half of the children with a history of choking have no FB in the airways. Fiberoptic bronchoscopy, which can be performed under local anesthesia with mild sedation, is the procedure of choice to ascertain the diagnosis. Rigid bronchoscopy remains the safest technique for extraction. Fiberoptic bronchoscopy should always be performed by a skilled operator able to convert to rigid tube extraction. FBA is less common in adults and can remain silent for a long time. In contrast to children, fiberoptic bronchoscopy can usually be used for diagnosis and for extraction. This article will focus on the practical aspects of the management of children and adults with suspected FBA.

Tracheobronchial foreign body (FB) removal opened the era of bronchoscopy when Gustav Killian in Freiburg in 1897 extracted a pork bone from the trachea of a German farmer with an esophagoscope [1]. Since that time, epidemiological features and diagnostic techniques have changed, use of fiberoptic or rigid bronchoscopy has been debated, but the extraction techniques per se do not basically differ.

Epidemiology

Foreign Bodies in Children

Airway aspiration of an FB remains a common problem with life-threatening complications in small children. As a tertiary referral teaching hospital in a geographic area of 4.05 million inhabitants, we determined in children under 4 years of age an annual incidence of 25/100,000 of suspected FBs and 9/100,000 of verified FBs [unpubl. personal data]. FB aspiration (FBA) accounted for 7% of all accidental deaths in children under 4 years of age in the US during the year 1986 [2]. In pediatric series, 80% of patients were 3 years of age or younger, with the peak incidence of aspiration occurring during the second year of life [3–6], when children start to stand up, put things into the mouth, are not able to masticate well and have relatively inefficient airway protective mechanisms besides the habit of crying, laughing and playing during meals. The male/female ratio is between 1.7:1 and 2.4:1 [2–5]. FBs usually are vegetables: nuts and particularly peanuts (36–55%) or seeds, other food particles or pieces of toys [3–5, 7]. Preponderant right-sided location of the FB, as in adults, is not found in children. Cleveland [8] has reported that, in children, the left mainstem bronchus is closer in size to the right mainstem bronchus; in addition, the left mainstem bronchus does not branch at the same acute angle as in adults.

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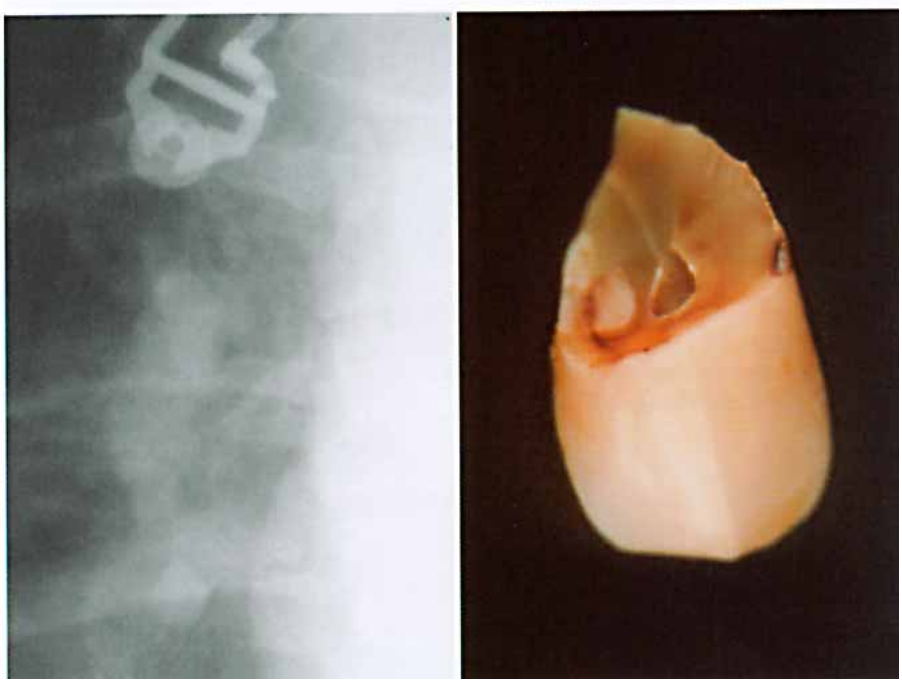

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Foreign Bodies in Adults

Tracheobronchial FBA is uncommon in adults. In the literature only 5 large series have been reported [7, 9, 10–12], compared to dozens of publications concerning children. The largest series, reported by the Mayo Clinic [10], identified 60 adults over a 33-year period. Two recent studies in Taiwan reported, respectively, 47 and 43 consecutive cases over a 13- and a 15-year period [11, 12]. In our institution, FBA in adults accounts for less than 2‰ of final diagnoses out of 4,500 bronchoscopies/year. In contrast, we see 15–25 cases in children (<15 years) annually. In children, nuts account for the large majority of FBs whereas in adults, the nature of FBs is highly variable (fig. 1, 2). Aspiration of nails or pins mostly occurs in

young or middle-aged adults during do-it-yourself activities. Aspiration of dental debris, appliances or prostheses usually complicate facial trauma (fig. 3) or dental procedures. Neurological disorders, loss of consciousness complicating trauma, alcohol or sedative abuse classically predispose to aspiration of food fragments. The type of the aspirated food fragments itself depends on local customs. For instance, in Western, Chinese and Middle east populations, vegetable matters [10], bones [11, 12] and watermelon seeds [13] are, respectively, the most frequently aspirated food particles. One peculiar syndrome in adults, referred to as the cafe coronary [14, 15] consists in fatal or near fatal food asphyxiation occurring during a meal while eating incompletely chewed meat. This generally occurs in the elderly with dentition problems, or swallowing disorders [16–19] or parkinsonism [20]. The estimated incidence of the cafe coronary syndrome is 0.66/100,000 [20].

Table 1. Signs and symptoms revealing a respiratory FB

History of choking
Recurrent wheezing
Hemoptysis
Chronic cough
Unilaterally decreased breath sounds
Overinflated lobe or lung
Atelectasis
Pneumothorax
Pneumomediastinum, subcutaneous emphysema
Recurrent pneumonia in the same area
Bronchiectasis
Lung abcess
Pleuresis

Diagnostic Approach to Foreign Bodies

Clinical Features and Diagnostic Work-Up in Children

A witnessed episode of choking (sudden onset of spelling cough and/or dyspnea and/or cyanosis in a previously healthy child) has a high sensitivity: 79–88% [2, 4, 5, 21]. Whenever there is a history of choking, tracheobronchial examination is necessary, even in the absence of physical or radiographic change. Physical findings can be absent in up to 39% of patients with FB [7], and radiographs are normal in 6–38% of patients [2, 5, 7, 21–24]. A history of choking is sometimes disregarded. In the series of Blazer et al. [25], as much as 18% of all children arrived at the hospital more than a month after aspiration; although a history of choking was present in 73% of these children. Among 125 patients with such a history in the series of Wiseman [22] only 52% were diagnosed early. In those few children who were not witnessed to choke, the diagnosis is often delayed.

Signs and symptoms that should evoke FBA are listed in table 1. Once evoked, there is no question that tracheobronchial examination is the key-stone to confirm the diagnosis. Three strategies can be proposed. The first and oldest one is to start systematically with rigid bronchoscopy because it allows both diagnosis and extraction with excellent safety. The second is to promote fiberoptic bronchoscopy under local anesthesia as first diagnosis procedure when there is a low probability of an airway FB, and so to avoid numerous rigid bronchoscopies under general anesthesia to reduce cost and length of hospitalization. If an FB is present, extraction is then immediately performed with the rigid bronchoscope. An alternative strategy, consisting in performing fiberoptic bronchoscopy after tracheal intubation and under general anesthesia for

Table 2. Diagnostic value of patient's history of choking, physical and chest X-ray findings in children with suspected FBA [adapted from ref. 4, 5, 21]

	PPV	Se	Sp	NPV
History of choking	50/63/78	85/79/81	21/46/33	60/64/38
Unilaterally decreased breath sounds	84/84/–	65/67/–	88/85/–	73/68/–
Wheezing	65/47/74	33/10/60	84/87/40	57/45/26
Radiopaque FB	100/100/–	20/7/–	100/100/–	57/47/–
Unilateral obstructive emphysema	81/86/–	53/55/–	88/89/–	67/63/–
Abnormal inspiratory X-ray	72/–/83	70/–/82	74/–/44	73/–/41

PPV = Positive predictive value; Se = sensitivity; Sp = specificity; NPV = negative predictive value; – = no data. Results are indicated in the following order of studies: Martinot et al. [5], François et al. [4] and Hoeve et al. [21].

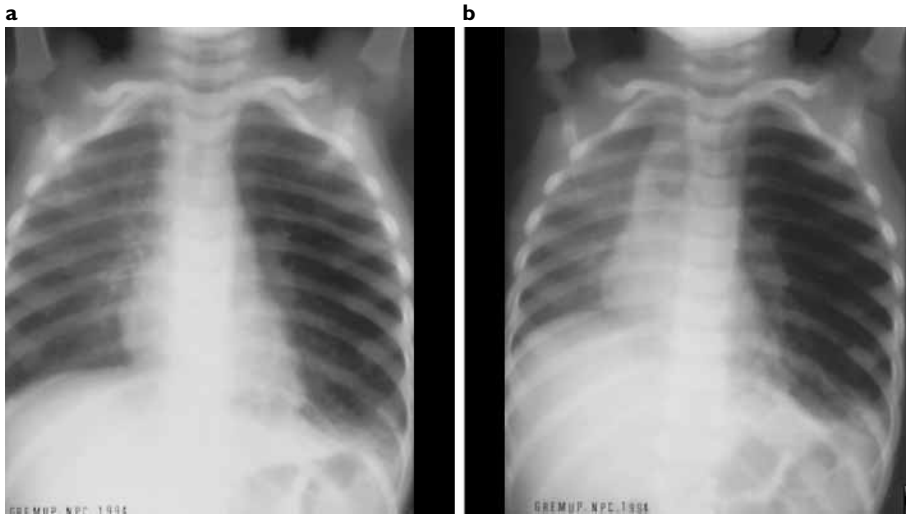

Fig. 4. FB impacted in the left mainstem bronchus of a 2-year-old child. Obstructive emphysema during inspiration (**a**) and markedly increased during expiration (**b**).

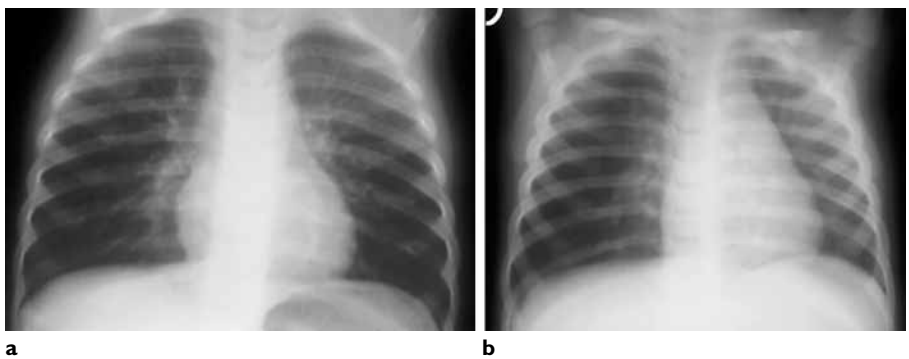

Fig. 5. FB impacted in the right mainstem bronchus of a 1-year-old child. Inspiratory chest X-ray normal (**a**). Obstructive emphysema present during expiration (**b**).

diagnosis and extraction [26] will be discussed below. Besides a chest X-ray, other explorations such as a V/Q or a CT scan seldom contribute to the diagnosis [27, 28]. To determine the best strategy, one needs to evaluate the probability that an FB is present, i.e. to estimate the probability that endoscopy will be therapeutic.

In the literature, all but three articles [4, 5, 21] studied cases with definite FBA (excluded cases with suspected FBs), and thus could only investigate the sensitivity of clinical and radiological findings. In two studies [4, 21] the diagnostic value of clinical and radiological signs were calculated on retrospective data. In the study that we conducted [5], physical and chest X-ray findings were noted before endoscopy. Diagnostic values of patient's history of choking, physical and chest X-ray findings are summarized in table 2. From these data, we can infer that a history of choking has a high sensitivity (79–85%), but a low positive predictive value (PPV). Obstructive emphysema (fig. 4), especially when associated with ipsilateral decreased breath sounds, has a very high PPV. In children with a normal inspiratory chest X-ray (fig. 5), an expiratory chest X-ray or fluoroscopy is worth being performed. We thus recommend that, for diagnosis, fiberoptic bronchoscopy should be performed first [5], except when asphyxia, radiopaque FB (fig. 6) or unilaterally decreased breath sounds plus obstructive emphysema are present (fig. 7). If one of these three items is present, the diagnosis of FBA is highly probable (PPV >90%), and rigid bronchoscopy can be proposed as first-line examination [5].

Clinical Features and Diagnostic Work-Up in Adults

In contrast to children, there is no prospective study which evaluates the diagnostic values of clinical and radiological signs in adults with suspected FBA. Therefore, the available information derives from retrospective series of definite cases of FBA. Acute presentation in adults is seldom, the reason being that in most cases the FB is wedged distally (lower lobe bronchi or truncus intermedius) whereas in children the FB usually obstructs proximal airways (mainstem bronchi). Therefore dyspnea is rarely reported by adults. In the series of Lan [11], shortness of breath was present in only 25% of the cases.

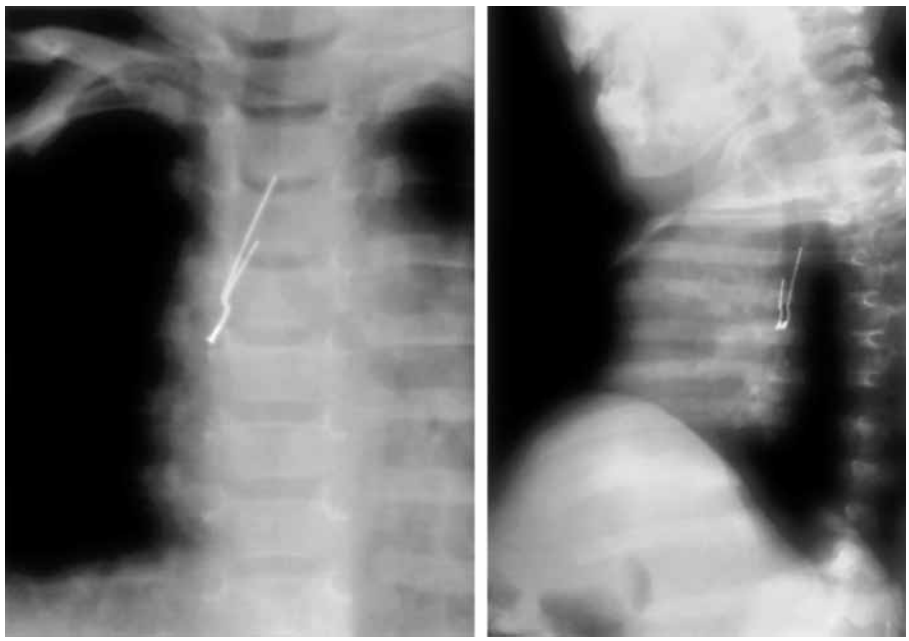

Fig. 6. Radiopaque FB in a 1-year-old child.

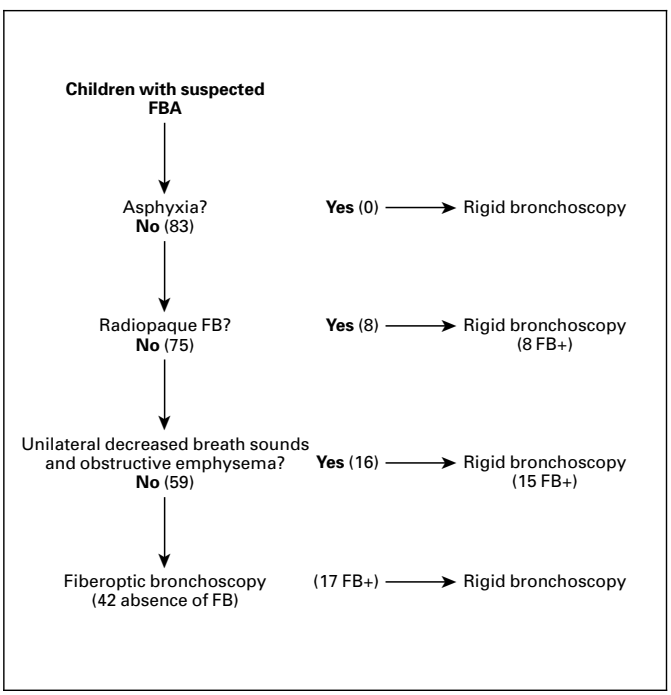

Fig. 7. Proposed management algorithm for children with suspected FBA and simulated results when applied retrospectively in the study population. [Adapted from ref. 5, with permission.]

In addition, in contrast to children, adults do not always volunteer or recall a history of choking [11, 12, 19, 29]. In fact, except in the cases where patients or witnesses report a typical choking episode and in the cases of radiopaque FBs, the diagnosis may be disregarded for a while by patients and doctors, due to the poor specificity of clinical and radiological signs. Thus, in adults, silent FBA may be a fortuitous finding of fiberoptic bronchoscopy performed because of symptoms such as chronic cough, hemoptysis, recurrent or nonresolving pneumonia or asthma not responding to therapy (fig. 8), which leads to suspicion of endobronchial abnormalities.

As shown above, in children, we recently resolved the question of 'how equivocal the diagnosis of FBA has to be before fiberoptic bronchoscopy is the initial investigation' [30] in a prospective study in 83 children referred for suspected FBA [5].

There is no question regarding the diagnostic utility of fiberoptic bronchoscopy in adults. From a practical viewpoint, however, two points must be stressed here. First, because of the potential risk of wedging the FB into a distal position, removal should not be attempted during a diagnostic bronchoscopy, unless the operator is skilled in the extraction technique and has the appropriate equipment at his disposal. In our experience, soft beans and soot bronchial plugs (fig. 9) are the only FBs that can be removed by simple suction. Second, as in children, in

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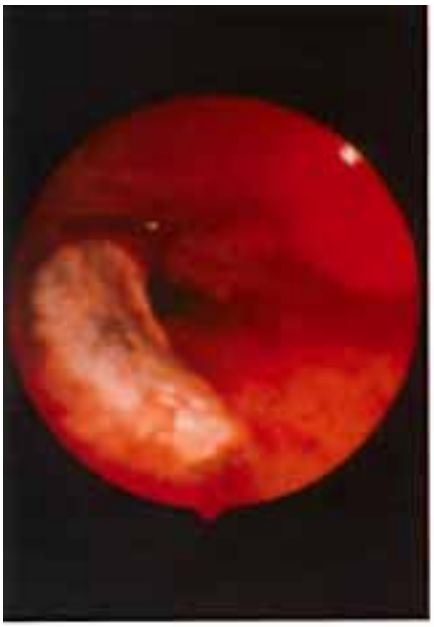

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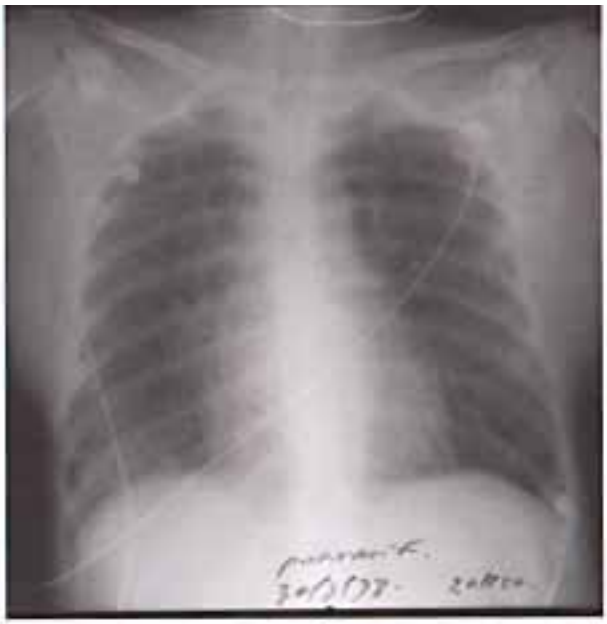

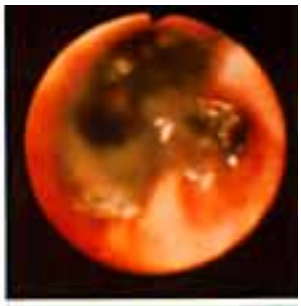

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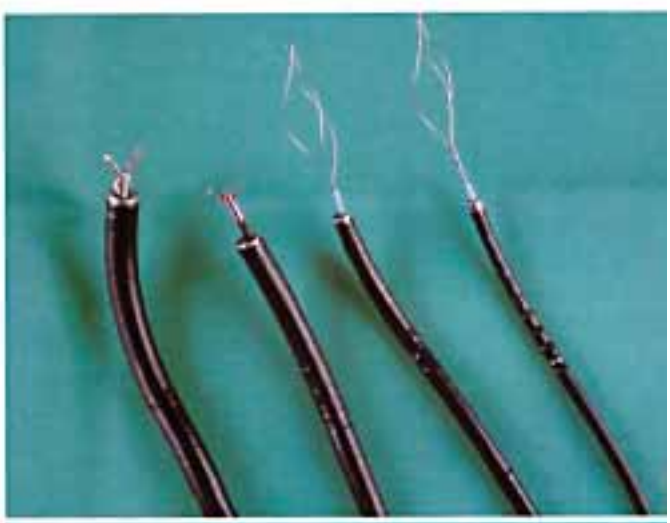

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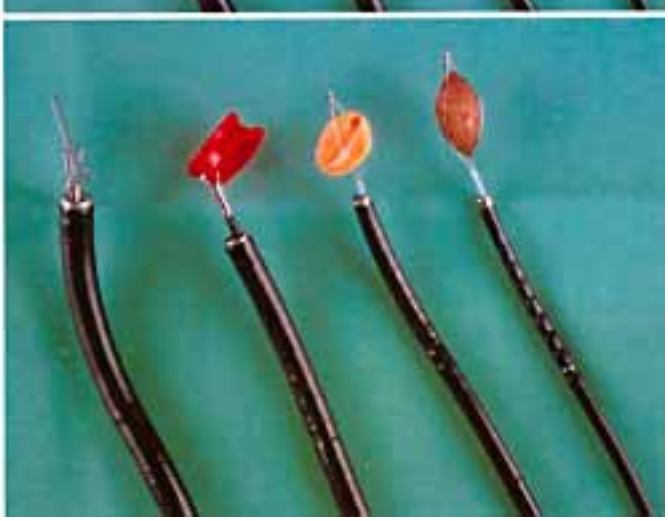

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Fig. 8. Sixty-eight-year-old lady with recent asthma unresponsive to antiasthma therapy. Endoscopic view showing an oyster shell fragment impacted in the right lower lobe bronchus.

Fig. 9. Severe burns in a 53-year-old man on mechanical ventilation because of acute respiratory failure; high inspiratory pressures. Chest X-ray showing overinflated lungs (**a**). Endoscopic view showing proximally impacted soot plugs (**b**). Large soot plugs moulding the right upper lobe removed by simple suction with a flexible bronchoscope (**c**).

Fig. 10. a From left to right: 6-mm outer diameter (OD) bronchoscope with a 2.8-mm diameter working channel (WC); 4.9-mm OD bronchoscope with a 2.2-mm diameter WC; 3.5-mm OD bronchoscope with a 1.2-mm diameter WC and 2.7-mm OD bronchoscope with a 1.2-mm diameter WC (Olympus prototype). **b** A large variety of ancillary equipment (forceps, grasping claws and baskets) can be passed through these bronchoscopes to grip various FBs.

cases of asphyxiating FBs, the bronchoscopist performing the diagnostic bronchoscopy must be able to convert immediately to the extraction procedure.

Diagnostic Fiberoptic Bronchoscopy, Technical Aspects

Diagnostic fiberoptic bronchoscopy for suspected FBA has no particular technical aspects. Fiberoptic bronchoscopy allows precise identification of nature and localization of FBs, facilitates the choice of size of rigid bronchoscopy and type of forceps, and thus contributes to shorten-

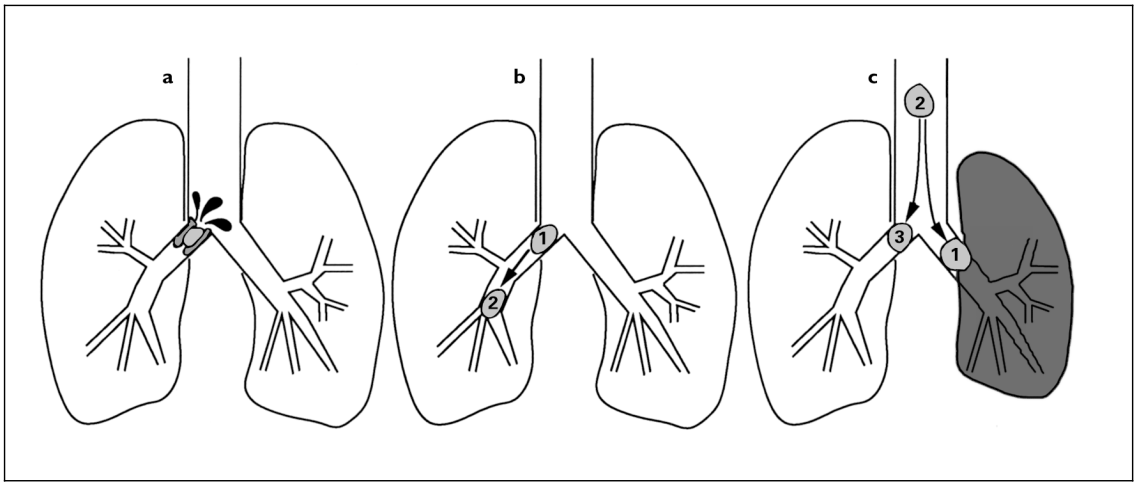

Fig. 11. Potential pitfalls of FB extraction. **a** Difficulties in grasping a right mainstem bronchus FB encased in bleeding bulky granulomas. **b** Accidental wedging of the FB into a distal position. **c** Postobstructive left lung atelectasis, accidental loss of the FB which suddenly obstructs the contralateral mainstem bronchus (risk of asphyxia).

ing the rigid bronchoscopy procedure. The bronchoscopes with 4.9 mm outer diameter with a 2.2-mm diameter working channel are used in patients older than 12 years. The bronchoscopes with 3.5 mm or even 2.7 mm outer diameter (Olympus prototype) with 1.2-mm diameter working channels are available for younger patients (fig. 10). The operator must be aware that, even in cases of a stable respiratory situation, the patient may decompensate during the diagnostic procedure due to accidental dislodgement of the FB (fig. 11). This justifies that, when FBA is suspected, fiberoptic bronchoscopy should be performed in a room fully equipped for resuscitation. Fiberoptic bronchoscopy can be performed under local anesthesia in most of the patients. In children, we also use intravenous sedation (midazolam 0.3 mg/kg). Thus, as shown above, most patients including children, with suspected FBA, can be managed for their diagnosis on an outpatient basis.

Foreign Body Removal: How to Do It

Timing of the Procedure

Bronchial obstruction by an FB may result in potentially serious complications including asphyxia, hemoptysis, postobstructive pulmonary infections and bronchiectasis [10–12, 31]. Organic FBs, particularly oily material such as peanuts elicit severe mucosal inflammation with bulky granulation tissue formation within a few hours (fig. 12). This can also be seen with chronically impacted sharp or rusty FBs. Therefore, once the diagnosis is established, extraction must be performed without delay. However, when an FB is completely encased in bulky and bleeding granulation tissue, extraction can be very difficult and unrewarding (fig. 11a). In these cases, provided the FB is well tolerated, it may be wiser to postpone extraction and give a short course (12–24 h) of intravenous corticosteroids (1–2 mg/kg prednisolone or equivalent) [23]. Although this attitude is not validated, in our experience, this usually results in dramatic 'melting' of the inflammatory reaction, thereby facilitating FB extraction.

Available Techniques

FB removal usually relies on bronchoscopic techniques. However, in young and healthy adults with a small movable FB (fruit pip or bead), positional manoeuvres (lateral decubitus and Trendelenburg) are worth to be attempted before bronchoscopy, in order to obtain spontaneous expectoration of the FB.

Rigid bronchoscopy is usually preferred for FB removal. The rigid bronchoscope provides a large access to the subglottic airways, ensuring correct oxygenation and easy passage of the telescope and grasping forceps. General anesthesia with short-acting agents such as propofol, allowing jet ventilation or manually assisted spontaneous

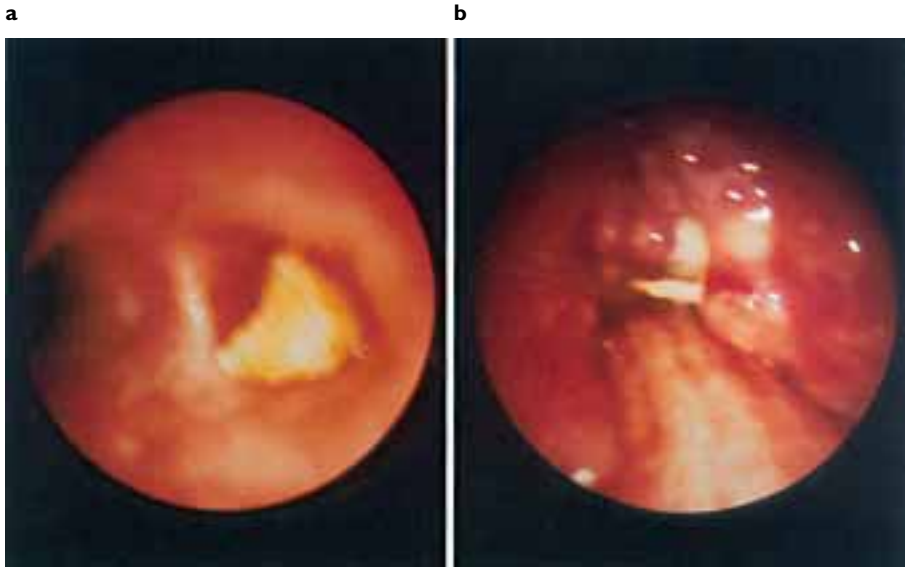

Fig. 12. **a** Half peanut recently (4 h) impacted in the right mainstem bronchus of a 13-month-old child. **b** Same problem, but choking occurred for 28 h. The oily peanut has caused severe mucosal inflammation with bulky granulation tissue.

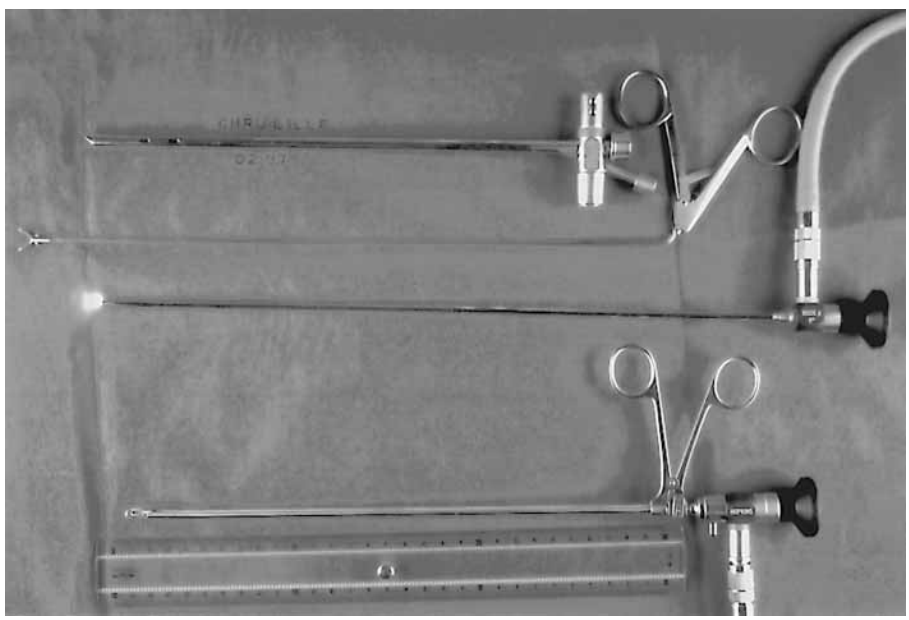

Fig. 13. From top to bottom: rigid bronchoscope, rigid FB forceps, rigid telescope, optical forceps.

ventilation, is safe and seldom exceeds 10 min. An optical forceps (fig. 13) allows a direct and clear vision of the FB and optically guided grasping. For lack, a rigid telescope and a forceps can be used coaxially through the bronchoscope (fig. 13). During the extraction procedure, one should always pay attention not to push the FB distally with the bronchoscope, the forceps or the suction catheter (fig. 11b). If present proximal to the FB, blood and secretions are carefully suctioned, and epinephrine (0.25 mg) can be instilled in order to retract swollen mucosa encasing the FB. The optical forceps is then advanced in the bronchial axis, a few millimeters proximal to the FB. For smooth and rounded FBs, the principle is to grip the largest volume of the FB. To achieve this, the smooth forceps (FB forceps) are preferred to the sharp alligator forceps (fig. 14a–d). The cups of the forceps are opened as much as possible (fig. 14a, b), and the forceps is advanced under visual control without pushing the FB downwards. The FB is then gently but securely gripped. Optical forceps and FB are then pulled up, a few millimeters distal to the tip of the bronchoscope, and the whole is then withdrawn en masse from the trachea. In case of large and hard FBs

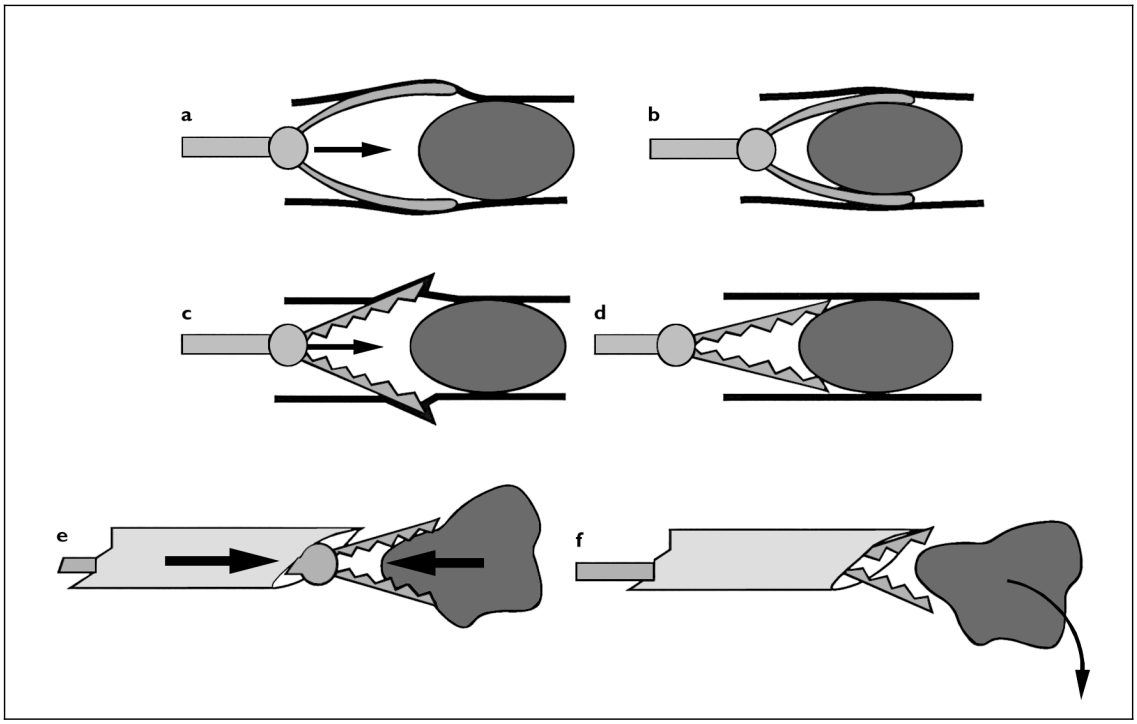

Fig. 14. Firm and atraumatic grasping of a smooth and rounded foreign body with an FB forceps (**a**, **b**). Traumatic and unsecured grasping with an alligator forceps (**c**, **d**). Risk of loosing the FB during extraction in cases of inappropriate coaxial movement between the bronchoscope and the forceps, pushing the foreign body out of the cups or jaws of the forceps (**e**, **f**).

such as pistachio shells, breaking the FB into 2 or 3 fragments may help extraction. However, too strong grasping of friable FBs such as peanuts should be avoided since it entails a risk of distal wedging of the small fragments (fig. 15). For heavy FBs, such as metallic FBs, which tend to move distally due to gravity, it may be helpful to place the patient in the Trendelenburg position. Alligator forceps are preferably used for grasping sharp or irregular FB. During the last step of extraction, FB can be lost accidentally, either because it is blocked in the narrow glottic area or because there was some inappropriate coaxial movement between the bronchoscope and the forceps, the tip of the bronchoscope pushing the FB out of the cups or jaws of the forceps (fig. 14e, f). If the case arises, before reintubating the trachea with the bronchoscope, one should first carefully inspect the oral cavity and the larynx with the laryngoscope in order to possibly catch the FB with a Magill forceps. Once the FB is removed, the trachea is reintubated with the rigid bronchoscope and careful examination is performed, as best with the fiberoptic bronchoscope passed through the rigid tube to check for the absence of another FB [32] or residual fragments. When managing food asphyxiation (generally with meat), one should always be aware that in about one third of the cases [20] the FB is indeed impacted at the glottic or subglottic level. Such proximally encased meat pieces can be easily pulled out with a Magill forceps (fig. 16) or for lack, in the field, digitally by sticking the middle and index fingers down the throat to grip the piece of meat [15].

A large variety of ancillary equipment (forceps, grasping claws, baskets and magnets) is available for FB extraction through fiberoptic bronchoscopes (fig. 10). Therefore, from a technical point of view, fiberoptic bronchoscopy can be used as an alternative to rigid bronchoscopy. Several authors have demonstrated that FBs, even large ones, can be effectively removed with pediatric fiberoptic bronchoscopes in children [26, 33–35].

Advantage and Drawbacks of Each Technique

The technique for removal of the FB depends on the nature and the size of the FB and on the age and the respiratory status of patient. In adults and even in children

over the age of 12, the available ancillary equipment makes it easy to remove most FBs with a 4.9-mm (or more) outer diameter fiberoptic bronchoscope, under local anesthesia. We agree with Limper and Prakash [10] that fiberoptic bronchoscopy is superior to rigid bronchoscopy in cases of distally wedged FBs, in mechanically ventilated patients or in cases of spine, jaw or skull fractures preventing rigid bronchoscope manipulation. The success rates of the fiberoptic bronchoscopy extraction technique in adults ranges from 60 to 90% [10–12]. It should however be stressed that the fiberoptic bronchoscopy extraction technique can be cumbersome and unrewarding and sometimes requires several attempts or a switch to rigid bronchoscopy to achieve extraction [10–12]. In addition, as illustrated in figure 11, the fiberoptic bronchoscopy extraction technique entails three risks. First, unsuccessful attempts to remove the FB may result in pushing the FB into a wedged position. Second, inflammatory lesions encasing an FB bleed as soon they are touched. Thus, removal with the fiberoptic bronchoscope may be cumbersome since suctioning blood and passing the grasping instrument through the working channel at the same time is impossible. Third, in cases of an impacted FB obstructing a mainstem bronchus with associ-

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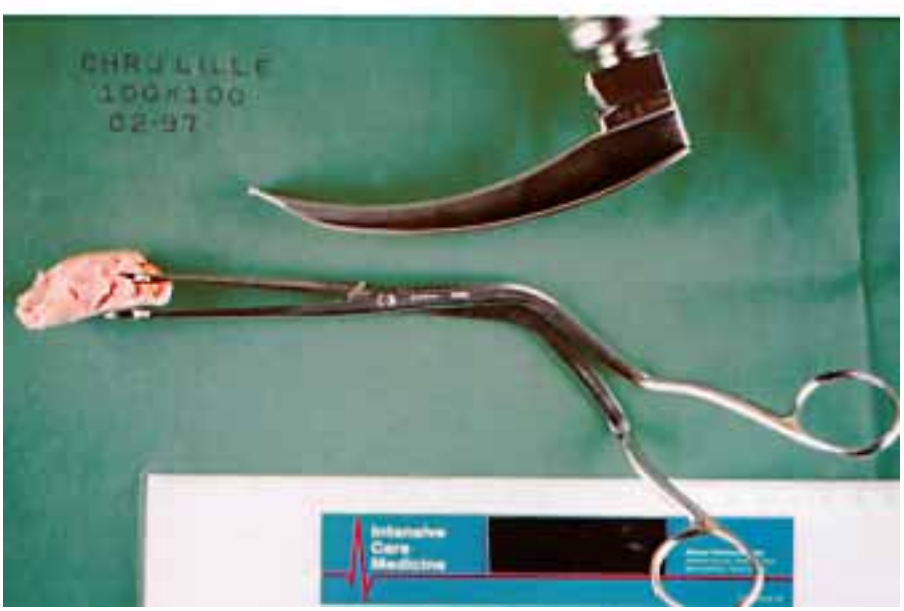

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Fig. 15. a Half peanut grasped with an optical forceps. **b** Accidental crushing of the peanut.

Fig. 16. Near fatal food asphyxiation (piece of meat). Emergency extraction under laryngoscopic examination with the Magill forceps.

ated lung atelectasis, accidentally loosing the FB in the contralateral lung, due to insufficient grasping with the fiberoptic forceps, is potentially lethal. As underlined by Castro et al. [26] the happenstance that a FB escapes from the rigid forceps (rigid bronchoscopy) is less likely to occur than with the forceps, grasping claws and baskets used through fiberoptic bronchoscopes. For practice, in adults and children older than 12 years, we recommend that fiberoptic bronchoscopy under local anesthesia should be considered as first examination for diagnosis and extraction except in cases of asphyxiating FBs where rigid bronchoscopy should be considered first.

In young children, the extraction technique is still a subject of debate. Some doctors [26, 33–36] advocate the use of the 3.5-mm outer diameter pediatric fiberoptic bronchoscope (working channel diameter of 1.2 mm). Although FB extraction with the new pediatric ancillary equipment is feasible with such fiberoptic bronchoscopes, it should be stressed that extraction is usually performed under general anesthesia with the fiberoptic bronchoscope passed through an endotracheal tube. Thus, the advantage, compared to FB removal with rigid instruments, appears to be rather limited. In addition, the pitfalls of FB extraction by fiberoptic bronchoscopy summarized in figure 11 and in figure 14e may have tragic consequences in young children. Therefore, from an educational point of view, we and others [2, 5, 30, 37, 38] recommended that rigid-tube extraction should be considered as the technique of choice for removal of the majority of FBs in children.

Complications of FB Extraction

Pre- and postinterventional complication rates of rigid bronchoscopy in children with suspected FBA range from 2 to 19% [3, 4, 24, 39], but include various complications such as hypoxemia, bronchospasm, laryngeal edema, cardiac arrhythmias or even complications related to the FB and not to the bronchoscopy: pneumonia or persistent atelectasis [3, 4]. In our experience, the rate of postoperative complications for rigid bronchoscopy was 16% including laryngospasm (n = 1) and laryngeal edema (n = 6) requiring brief intubation in 2 children [5]. Perez and Wood [30] suggested that if rigid bronchoscopy does not show an FB, but there is still a high degree of suspicion, then fiberoptic bronchoscopy can be passed through the rigid tube for inspection of more distal airways. The dislodgement of the FB as a result of fiberoptic bronchoscopy was not observed in the study of Wood and Gauderer [37] in 52 children. In our experience, this complication was observed once in 55 children undergoing diagnostic fiberoptic bronchoscopy [5]. One should therefore always keep this risk in mind and be able to convert to rigid-tube extraction.

Perioperative Management

The current controversy regarding the need for corticosteroids or antibiotics in the perioperative management of FBA results from the absence of comparative controlled studies. We and others [23] recommend the use of a short course of corticosteroids before FB removal when a well-tolerated FB is encased in bulky and bleeding granulation tissue. The preventive use of corticosteroids before bronchoscopy to decrease the incidence of postoperative subglottic edema has never been validated. When postoperative subglotting edema occurs, parenteral corticosteroids and/or aerolized epinephrine is usually recommended. Antibiotics are indicated only in cases of clinically, radiologically or bronchoscopically documented respiratory tract infection. The risk of laryngospasm within a few minutes after bronchoscopy justifies special attention in small children and, if necessary, immediate reintubation. Once the FB is removed, the whole tracheobronchial tree should be checked for the presence of another FB [32] or residual fragments. To do so, the trachea is reintubated with the rigid bronchoscope and careful examination is performed, at best with the fiberoptic bronchoscope passed through the rigid tube. If doubt persists, fiberoptic bronchoscopic examination may be recommended a few days later.

Conclusion

Clinical signs in children are usually highly suggestive. However, almost half of the children with a typical history of choking have no FB in the airways. Therefore, fiberoptic bronchoscopy is a safe and cost-saving diagnostic procedure [5, 37]. This procedure avoids unnecessary general anesthesia and reduces hospital stay. Even if fiberoptic bronchoscopy detects an FB in a child which needs subsequent rigid bronchoscopy for removal, this does not lengthen hospital stay as the second procedure immediately follows the first one [5]. For the majority of FBs in children, rigid-tube extraction remains the technique of choice for removal. In any case, diagnostic and therapeutic procedures should be performed by a skilled operator in a room equipped with full resuscitation equipment.

In adults, the diagnosis of FBA is often equivocal and sometimes even silent. In contrast to children, fiberoptic bronchoscopy may usually be used both for diagnosis and treatment.

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Therapeutic Bronchoscopy

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Laser Bronchoscopy

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Summary

This chapter is based on our 17-year experience with laser bronchoscopy. In addition to relevant background information, it contains a description of our technique and results. Suitability of a laser for therapeutic bronchoscopy depends on power density, absorption/scattering ratio in soft tissue and delivery system. Currently the Nd:YAG and Nd:YAP are the most suitable laser systems. Knowledge of tracheobronchial anatomy is essential. Since the volume of the airways is only 150 cm^3, accumulation of blood and secretions can lead rapidly to hypoxemia. The tracheobronchial tree contracts close relations with mediastinal vessels and perforation can be fatal. Safety depends on the skill and cooperation of the laser team. Laser bronchoscopy should be performed using a surgical bronchoscope under general anesthesia. Mechanical resection helps to reduce laser exposure and risk of perforation. The main indications for laser bronchoscopy are malignant tumors and tracheal stenosis. Location and extrinsic compression are the most important factors for the outcome in patients with malignancies. Endoscopic treatment must be associated with dilatation and stenting for effective treatment in patients with tracheal stenosis. Restoration of airway patency with immediate symptomatic improvement is achieved in 93% of cases overall.

With the exception of foreign body removal, applications for conventional bronchoscopy are diagnostic including direct visualization of the tracheobronchial tree, biopsy of lesions and specimen collection for culture and cytology. In this regard, the flexible fiberscope has greatly extended the range of application in comparison with rigid endoscopy.

The modern era of interventional bronchoscopy was born with the advent of lasers and has been characterized by a comeback of the rigid bronchoscope. The first endoscopic laser resections were performed by Godard et al. [1], Toty et al. [2] and Dumon et al. [3] in the early 1980s and were soon followed by other therapeutic modalities such as cryotherapy, electrocoagulation, brachytherapy and, most recently, stent placement.

Like any technique, endoscopic laser resection has limitations. However, it can be remarkably effective in well-selected indications and has provided a solution for previously intractable emergency problems and for some cases of iatrogenic tracheal stenosis. The purpose of this chapter is to describe our 17-year experience with laser bronchoscopy.

Bronchoscopic Lasers

The word 'laser' is an acronym for light amplification of stimulated emission of radiation. This name gives a succinct description of the process by which the laser beam is obtained. An external energy source, usually optical or electrical, is used to stimulate an active substance contained within the core of the laser so as to achieve a condition known as population inversion in which the population of atoms (or molecules) at some higher energy level is greater than the population at some lower energy level. For sustained laser action, population

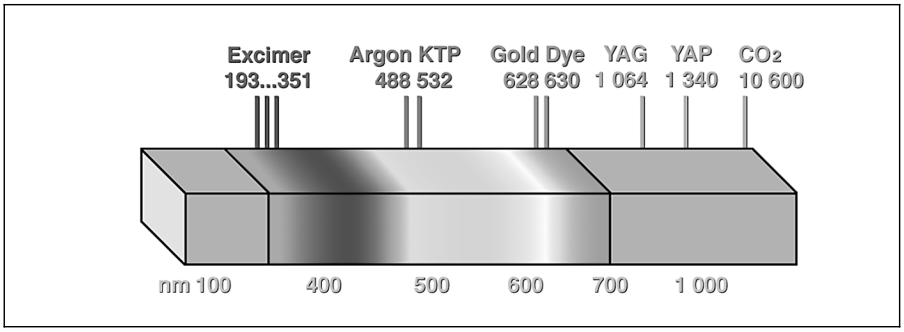

Fig. 1. Electromagnetic radiation spectrum. KTP = Potassium titanyl phosphate.

inversion must be great enough so that the amplification of photons by stimulated emission is greater than the attenuation of spontaneously emitted photons by absorption into unexcited atoms or molecules. The core of the laser, or pumping cavity, is designed with reflective walls which bounce emitted photons back into the active substance thereby producing new photons. The laser beam escapes through a partially reflective mirror placed at one end of the core.

Laser light has three unique characteristics, i.e. monochromaticity, coherence and collimation. Monochromaticity means that all light in the laser beam is of the same wavelength depending on the active element stimulated in the laser core. In order of decreasing wavelength and increasing frequency, electromagnetic radiation ranges from radiowaves to γ rays (fig. 1). Visible light is a narrow band from 400 to 700 nm between infrared and ultraviolet radiation. Coherence means that all waves in the beam are in step in time and space. Collimation means that the waves are traveling along parallel ray directions.

Although many lasers are now available and others are under development, devices differ with regard to their effects on the human body and are thus not equal in terms of their usefulness for medical applications. Three main characteristics determine the suitability of a particular laser for therapeutic bronchoscopy, namely: (1) power density rating, (2) ratio of absorption and scattering coefficients in soft tissue and (3) delivery system. Power density depends on laser technology and on factors such as target distance and exposure time. By determining the volume of tissue that is heated, absorption and scattering make the difference between cutting and hemostasis. Lasers with high absorption coefficients and low scattering coefficients are good scalpels, while those with low absorption coefficients and high scattering coefficients are good coagulators. The delivery system is important because of the limited size of the endoscopic working channel. Only lasers with optical fiber delivery systems are suitable for bronchoscopic use.

The CO_2 laser was the first laser to be used in the airways. It generates an invisible infrared beam of 10,600 nm. Because of its high absorption coefficient, the CO_2 is an excellent cutting tool that has been used for drilling and resection of tissue everywhere in the body. However, its use for bronchoscopic applications has been limited by its poor coagulating properties and especially by the need for a cumbersome articulated arm delivery system.

The argon laser produces a blue-green beam with a wavelength of 488 or 514 nm. Since this wavelength is absorbed by hemoglobin, the argon laser is a good coagulator. It has been used mainly for treatment of angioma. The main drawback for bronchoscopic applications is poor cutting ability. The power density of the argon laser is low, and the fiber must be placed in contact with the tissue to achieve resection.

Dye lasers are devices in which the beam from a krypton, argon, ruby or Nd:YAG laser is passed through a liquid made of fluorescent organic dyes such as rhodamines. The main application for dye laser technology has been to activate hematoporphyrin for photochemotherapy of in situ carcinoma, early-stage carcinoma and submucosal component of invasive carcinoma. Low-power dye lasers are not suitable for therapeutic bronchoscopy.

Excimer lasers are a special breed that produce ultraviolet wavelengths at 193, 222, 248, 308 and 351 nm using various rare gases including argon fluoride, krypton chloride, krypton fluoride, xenon chloride and xenon fluoride, respectively. Ultraviolet radiation is strongly absorbed by living tissue, but unlike infrared and visible red light, it is not converted into heat. Instead tissue destruction results from mechanical effects. The lack of collateral thermal damage to adjacent tissue is an advantage for some applications, but poor coagulation is a major limitation for bronchoscopic resection.

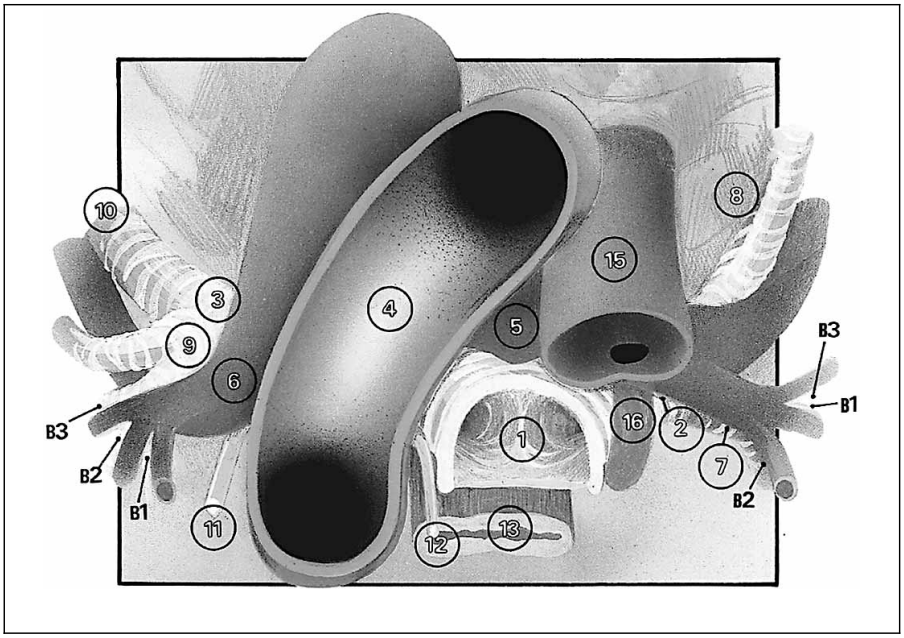

Fig. 2. Anatomical relationships of the tracheobronchial tree. 1 = Trachea; 2 = right mainstem bronchus; 3 = left main stem bronchus; 4 = aorta; 5 = right pulmonary artery; 6 = left pulmonary artery; 7 = right upper lobe bronchus; 8 = troncus intermedius; 9 = left upper lobe bronchus; 10 = left lower lobe bronchus; 11 = vagus nerve; 12 = recurrent nerve; 13 = esophagus; 15 = superior vena cava; 16 = azygos vein; B1–3 = segmental bronchi of upper lobes.

Diode lasers represent a new technological concept. Laser radiation is obtained by passing an electrical current through a solid-state semiconductor diode. By simplifying the laser cavity, this technology has allowed the design of high-powered devices in compact, air-cooled cabinets. Aluminium gallium arsenide diode lasers emit beams up to 60 W at a wavelength of 810 nm allowing fairly good cutting and hemostasis. This technology has not been widely used for therapeutic bronchoscopy.

The Nd:YAG (neodymium:yttrium aluminium garnet) laser with an invisible infrared beam (wavelength 1,064 nm) exhibits a number of advantages for endoscopic use. It can deliver up to 100 W of output in the beam through a flexible quartz fiber. It is an inherently durable, reliable laser with minimal servicing. It seems to have a virus-killing effect which may be a significant advantage for the treatment of tumors like papillomas [4]. For these reasons, the Nd:YAG is probably the most widely used laser device for therapeutic bronchoscopy.

A remarkable feature of the Nd:YAG is its sensitivity to tissue pigmentation. Surface absorption is low in lightly colored tissue and high in darkly colored tissue. In practice, this means that a large volume of lightly colored tissue can be 'cooked' to achieve hemostasis by denaturation and agglomeration of tissue proteins, shrinkage of connective tissue like collagen and extensive edema. To perform resection, it is simply necessary to induce charring, so that surface absorption increases and vaporization proceeds rapidly. Charring may be obtained by increasing the power density or by inducing surface bleeding to darken the surface. Some Nd:YAG lasers feature the superpulsing mode that can deliver short high-powered pulses (300 W) in rapid succession and frequency doubling using a potassium titanyl phosphate crystal that provides a 532-nm green beam similar to that of an argon laser. Superpulsing facilitates cutting and frequency doubling enhances coagulation.

A recent addition to the biochemical laser family with potential for therapeutic bronchoscopy is the Nd:YAP (neodymium: yttrium aluminum pevroskite) laser with a wavelength of 1,340 nm. Absorption in water is 20 times greater for the Nd:YAP beam than the Nd:YAG beam. The Nd:YAP achieves particularly good coagulation.

Physiological and Anatomic Considerations for Endobronchial Laser Treatment

The volume of the tracheobronchial tree is only 150 cm^3 (anatomical dead space). Thus even a small amount of blood or secretion can cause major hypoxia leading to serious cardiovascular problems including arrhythmia, bradycardia, myocardial ischemia and even cardiac arrest. Maintaining a free airway and efficient ventilation at all times is essential for the prevention of these complications. With regard to ventilation, it should be stressed that

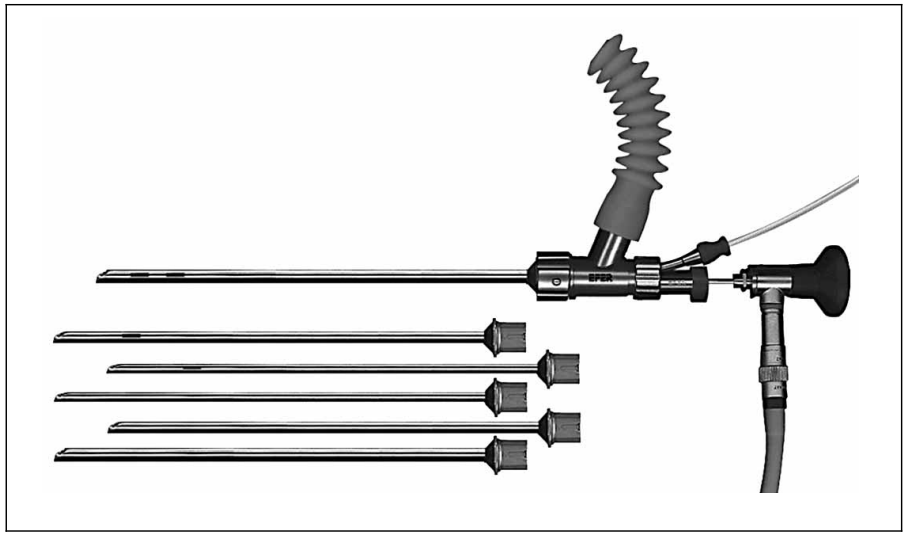

Fig. 3. Pediatric version of the EFER-DUMON therapeutic bronchoscope with interchangeable barrels.

proper precaution should be taken when using a laser in an enclosed oxygen-rich space containing inflammable materials such as a flexible fiberscope.

The topography of the tracheobronchial tree which consists of a succession of subdividing bronchi is familiar to pulmonologists. However, it is useful to recall the anatomical relationships of the tracheobronchial tree (fig. 2). The back of the trachea is in permanent contact with the front of the esophagus. The innominate artery crosses the front of lower third of the trachea. The aortic arch and the recurrent nerve are in contact with the left side of the bottom of the trachea.

The main stem bronchi are also easily accessible with the rigid bronchoscope. The right main stem bronchus is in contact with the pulmonary artery in the front. The left main stem bronchus is surrounded by the esophagus in the back, the aortic arch above and the pulmonary artery in the front. The upper lobe bronchi are in close contact with the pulmonary artery especially on the left.

The main anatomic relations of the right lower and middle lobe bronchi and the left lower lobe bronchi are the organs of the mediastinum, in particular the heart and pulmonary veins.

Basic Principles of Endoscopic Laser Bronchoscopy

Rigid Bronchoscopy Laser Resection

Because endobronchial laser treatment involves surgical resection, it is most safely performed with a surgical bronchoscope (fig. 3) under general anesthesia in a surgical setting with a nearby recovery room. The surgical bronchoscope is the key to safety since it allows simultaneous ventilation and treatment (aspiration, coagulation and debulking). Indeed, safe laser resection depends on preserving ventilation, preventing hemorrhage and minimizing laser exposure.

Table 1. Anesthesia protocol for laser resection

Induction	Maintenance
Fentanyl, 2.5 µg/kg Droperidrol, 125 µg/kg Propofol, 2.0 mg/kg Succinylcoline, 1.5 mg/kg	propofol, 7–8 mg/kg/h (reduced to 5– 6 mg/kg/h after 15 min); if necessary, fentanyl, 2 µg/kg + propofol, 0.5 mg/h

General anesthesia is usually more comfortable for both the patient and endoscopist. For the bronchoscopist, the ideal anesthetic technique should allow spontaneous ventilation while suppressing the cough reflex. Our anesthetic protocol is described in table 1. Anesthetic agents with short half-lives should be preferred so that the patient recovers rapidly, and postoperative ventilation is not needed. If muscle relaxants with Venturi jet ventilation or gas anesthesia are used, closed-circuit ventilation is required.

Regardless of the anesthetic technique, the endoscopist and anesthesiologist must work in close collaboration to safeguard ventilation throughout the procedure. Blood oxygen should be monitored using an oxymeter. A suction

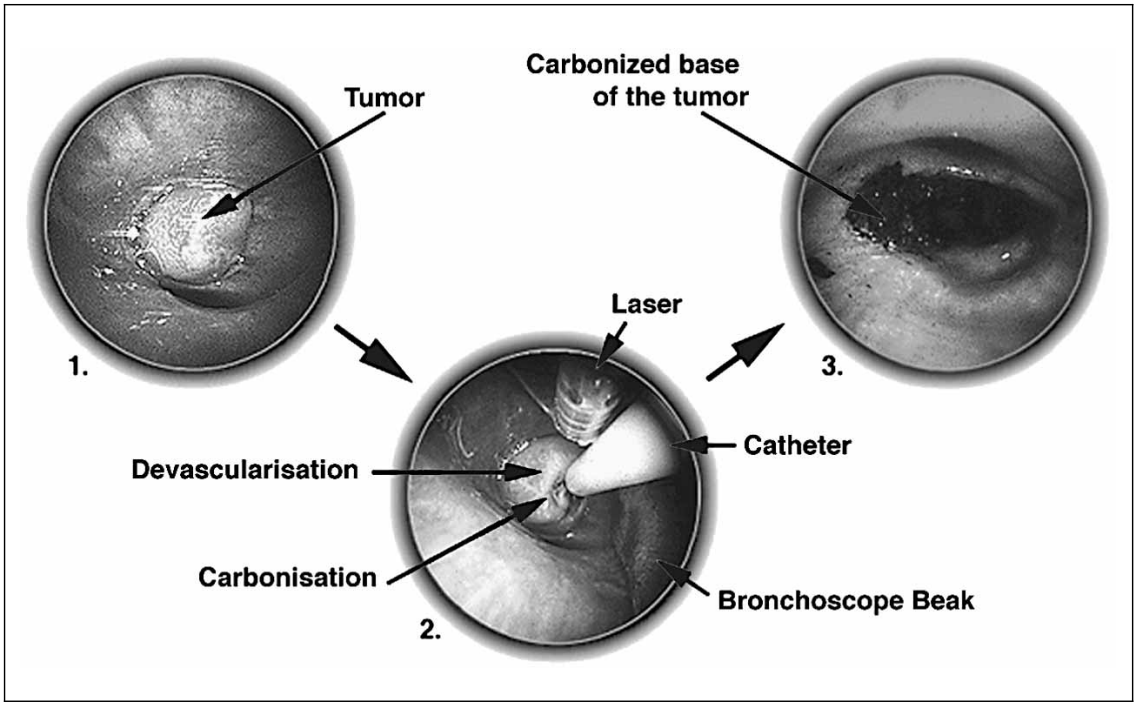

Fig. 4. Devascularization and vaporization using a laser.

catheter should always be in place at the site of treatment in order to keep the operating field clear by continuous suction of blood, secretions and smoke. The endoscopist should not hesitate to perform aspiration whenever necessary, even if resection must be momentarily interrupted. An in-depth description of the anesthetic management for interventional bronchoscopy is provided in the chapter by Studer and Biro.

To prevent hemorrhage, it is important to coagulate the lesion before resection. In this regard, it is essential to remember the basic rules for adjusting power density to achieve coagulation or resection. For the Nd:YAG or Nd:YAP, these rules can be summarized as follows:

(1) Dark areas having a higher absorption coefficient than light aras; in addition to blood supply, the main factor affecting tissue color during laser treatment is charring.

(2) Power density depends on the power setting of the laser and the distance of the tip of the optical fiber from the tissue:

$$\text{Power density} = \frac{\text{Power}}{\text{Spot diameter}}.$$

(3) Duration of emission also determines energy density which is the product of power density and time:

$$\text{Energy density} = \text{Power density} \times \text{time}.$$

Practically speaking, these rules mean that power density can be adjusted without changing power settings simply by moving the tip of the laser closer to or farther from the surface. Thus at a power setting of 30–45 W with an emission duration of 1 s, tissue shrinkage and therefore devascularization is obtained by holding the fiber about 1 cm from the target while charring and vaporization are obtained by holding the fiber about 3 mm from the target (fig. 4). It is important to note that fibers with metallic tips should always be used. Using bare fibers which have an irregular tip cross-section, laser light loses collimation and, as a result, aiming and control of power density become problematic.

Once a tumor has been coagulated or in order to avoid heating beneath the surface, laser exposure can and should be minimized using mechanical debulking with the tip of the bronchoscope, biopsy forceps, resector system and suction tube. So great is the importance of debulking with the tip of the bronchoscope that a more

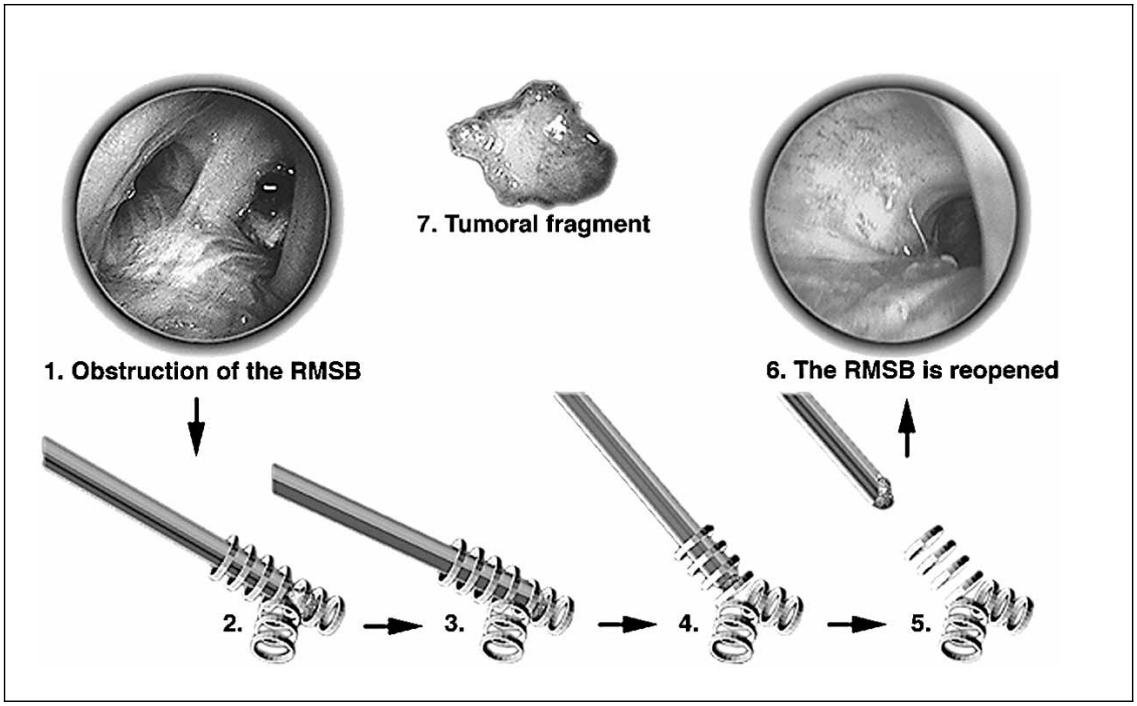

Fig. 5. Mechanical debulking with the tip of the bronchoscope. RMSB = Right main stem bronchus.

suitable name for the technique might be 'laser-assisted mechanical resection' (fig. 5). The axis of the bronchus can be located by tactile feedback from the bronchoscope in contact with bronchial cartilage. Mechanical debulking also shortens procedure times.

At the end of the procedure, the base of the lesion should be thoroughly coagulated using long, low-power pulses (20–30 W for 4–5 s). To avoid perforation, the beam should be fired tangentially to the wall in a continually scanning fashion.

Laser Fiberscopy

Most practitioners in the world, (Personne et al. [5], Vergnon et al. [6] and Dumon et al. [7] in France; Cavaliere et al. [8] in Italy; Diaz et al. [9] in Spain; Becker et al. [10] and Freitag et al. [11] in Germany; Bolliger [12] in Switzerland; Beamis and Shapshay [13], Edell and Cortese [14, 15], Gelb and Epstein [16] and Colt [17] in the USA) perform endoscopic laser resection using a rigid bronchoscope. However, a few Americans (Unger [18] and Mehta et al. [19, 20]) have reported excellent results using the flexible fiberscope. Tables 2 and 3 summarize the advantages and disadvantages of rigid bronchoscopic and flexible fiberscopic laser treatment.

Laser fiberscopy requires strict cooperation on the part of the patient who must be able to cope with the discomfort. Local anesthesia must be thorough and should be renewed if the procedure is prolonged. Care should be exercised when administering oxygen due to the risk of ignition of the fiberscope. The working channel must be perfectly clean (no trace of blood) when the laser fiber is inserted.

Small peripheral lesions are easy to treat under local anesthesia. After thorough coagulation, large pieces can be removed with biopsy forceps. Fragments should be stripped off with a downward rather than an upward movement. Fragments can be removed using accessories such as a Dormia basket or a Fogarty balloon. Mechanical removal greatly shortens the procedure.

Lesions in the main stem bronchi require great care. The patient should be turned on the obstructed side, so that ventilation of the healthy side can continue in case of hemorrhage.

Lesions in the trachea or in pneumonectomized patients are very difficult to treat with a flexible fiberscope. The major risks are hemorrhage and hypoxia, which are very difficult to control using the fiberoptic bronchoscope. Treatment of tracheal lesions confronts the endos-

Table 2. Advantages and disadvantages of flexible bronchoscopic laser technique.

Advantages	Disadvantages
Flexible fiberscopy is the most widely used endoscopic technique.[1]	Treatment is uncomfortable for the patient and time-consuming for the physician.
Flexible fiberscopy is an ambulatory procedure that can be performed under local anesthesia, thus avoiding the dangers of general anesthesia particularly in high-risk patients.	Exposure to smoke is hazardous for the staff and the patient.
Fiberscopy is less cost intensive since it does not require an operating room and can be done by a smaller staff.	The inability to perform mechanical resection and dilatation results in less complete disobstruction and makes it necessary to use more laser energy to vaporize the lesions.
	Because the working channel of the fiberscope is small, instruments (laser fiber, suction tubes, forceps) must be inserted one at a time.
	Bleeding is difficult to control.
	Fiberscopes and accessories are expensive and easily damaged (ignition).
	Stent placement is difficult under local anesthesia without previous dilatation.

[1] This argument is based on the dubious assumption that lung physicians are reluctant to learn new techniques.

Table 3. Advantages and disadvantages of rigid bronchoscopic laser technqiue

Advantages	Disadvantages
General anesthesia is more comfortable for the patient and the physician.	Procedures require experienced staff, skillful endoscopist, courageous anesthetist and trained instrumentalists.
Laser fiber, suction catheters and forceps can be introduced and used simultaneously.	Procedures must be performed in an operating room with a nearby recovery room.
Dilatation and mechanical resection can be used to shorten procedure time, diminish laser exposure and enable more complete disobstruction.	Need for hospitalization increases the cost.
Complications can be more easily controlled.	
Stent placement is simple.	
Equipment is inexpensive and indestructible.	

Table 4. Complications occurring during 5,049 therapeutic bronchoscopy procedures carried out between April 1982 and March 1997 (Cavaliere)

Complications	n	Deaths
Hemorrhage >250 cm^3	34	
Transient pneumothorax	25	
Transient mediastinal emphysema	16	
Respiratory failure	21	6
Cardiac arrest	17	6
Myocardial infarction	5	2
Pulmonary embolism	1	1

Mortality rate 3/1,000.

copist with the dilemma of choosing between vaporization to open the airway quickly and coagulation which is needed to prevent excessive bleeding during removal. The fiberscope should not be used in cases involving subtotal obstruction of the trachea.

Another important drawback of the flexible technique is the possibility of irreparable damage to the fiberscope. Indeed, sharp angulation can cause the optical fiber to break and, as a result, the working channel is burned when the laser is fired. In 300 laser procedures performed using the flexible system, Dumon destroyed 3 fiberscopes in this way [unpubl. data]. Given the price of a fiberscope, the risk can greatly increase the cost of treatment.

Table 5. Indications for laser bronchoscopy between April 1982 and March 1997 (Cavaliere)

Pathology	Patients	Treatments	General anesthesia	Local anesthesia
Airway tumor	2,481 (74)	3,524	3,159	365
Tracheal stenosis	499 (15)	950	800	150
Miscellaneous	360 (11)	575	391	184
Total	3,340	5,049	4,350 (86)	699 (14)

Rigid bronchoscope 91%, flexible fiberscope alone 9%, figures in parentheses are percentages.

Accident Prevention

The main risks of endoscopic laser resection are hypoxia, hemorrhage, perforation and fire. In accordance with the old adage 'an ounce of prevention is worth a pound of cure', the following rules should be respected: (1) avoid hypoxia by keeping peripheral airways free at all times; (2) avoid hemorrhage by coagulating lesions thoroughly before resection; (3) be mindful of the anatomical dangers and the biological effects of the laser; (4) prefer mechanical debulking to laser resection in order to limit iatrogenic complications; (5) use the laser in the discontinuous mode at a moderate power setting (40–45 W); (6) do not use the laser when ventilating the patient with pure oxygen (we advise a limit of 50%). Complications in our experience are summarized in table 4. Overall mortality was 3:1,000.

Indications for Laser Bronchoscopy

In theory, any obstructive lesion in the main airway, i.e. the trachea and/or the right and left stem bronchi, can be treated by therapeutic bronchoscopy. The main indications for laser resection are tumors and iatrogenic tracheal stenosis. Table 5 summarizes the indications for laser bronchoscopy under general and local anesthesia in our series.

Airway Tumors

Airway tumors may be subdivided into three histological groups: malignant, uncertain prognosis and benign. For malignant lesions, laser therapy is purely palliative and should be performed only in nonoperative cases. This having been said, it should be underlined that surgery is feasible in only 25% of lung cancer patients, and more than 70% of these patients have recurrences. Thus, more than 90% of lung cancer patients require palliative treatment. Laser resection is a therapeutic option for the 30% of these patients in whom lung cancer causes obstruction in the trachea and main stem bronchi with subsequent respiratory distress, bleeding and infection. Table 6 shows the number of patients and treatments corresponding to malignant airway tumors. Metastatic and rare tumors are detailed in tables 7 and 8, respectively.

Table 6. Malignant tumors treated by therapeutic bronchoscopy between April 1982 and March 1997 (Cavaliere)

Pathology	Patients	Treatments
Squamous cell	1,370 (66)	1,941
Adenocarcinoma	174 (8)	229
Small cell	117 (6)	135
Large cell	62 (3)	83
Unclassifiable	109 (5)	132
Metastatic	157 (8)	286
Rare tumors	80 (4)	109
Total	2,069	2,915

Figures in parentheses are percentages of series.

The category 'tumors of uncertain prognosis' regroups various tumors characterized by slow growth and low tendency to metastasis such as carcinoids, adenoid cystic carcinomas, paragangliomas etc. As for malignant tumors, laser therapy is mainly palliative. In some cases, it can also be used as a bridge to surgery and even achieve local cure for small tumors of low-grade malignancy. For example, laser surgery can be curative for strictly endobronchial carcinoids of typical histology. Conversely, typical carcinoid tumors with extraluminal extension are always surgical indications. Table 9 shows the number of patients and treatments corresponding to tumors with uncertain prognosis.

Benign tumors such as hamartoma, chondroma, leiomyoma and papilloma are excellent indications for laser

Table 7. Metastatic tumors treated by therapeutic bronchoscopy between April 1982 and March 1997 (Cavaliere)

Tumor location	n	Tumor location	n
Thyroid	43	Thymus	1
Kidney	32	Prostate	1
Colon	30	Testis	1
Esophagus	25	Bone	1
Breast	9	Liver	1
Melanoma	5	Larynx	1
Uterus	4	Ureter	1
Ovary	2		

157 patients – 286 treatments.

Table 8. Rare malignant tumors treated by therapeutic bronchoscopy between April 1982 and March 1997 (Cavaliere)

Tumors	n	Tumors	n
In situ carcinoma	27	Fibrosarcoma	2
Non-Hodgkin lymphoma	15	Fibrohystiocytoma	1
Hodgkin lymphoma	5	Teratoma	1
Carcinosarcoma	16	Myeloma	1
Sarcoma	4	Basaloid tumor	1
Malignant plasmacytoma	3	Glomic tumor	1
Leimyosarcoma	3		

80 patients – 109 treatments.

Table 9. Tumors with uncertain prognosis treated by therapeutic bronchoscopy between April 1982 and March 1997 (Cavaliere)

Pathology	Patients	Treatments
Carcinoid	129	170
Adenoid cystic	49	103
Mucoepidermoid	14	19
Spindle cell	5	10
Mixed	2	3
Paraganglioma	2	2
Cystoadenoma	2	2
Total	203	309

Table 10. Benign tumors treated by therapeutic bronchoscopy between April 1982 and March 1997 (Cavaliere)

Tumors	n	Tumors	n
Hamartoma	51	Leiomyoma	7
Papilloma	44	Myoblastoma	5
Amyloidosis	21	Plasmacytoma	4
Polyp	21	Fibrolipoma	3
Angioma	19	Fibroma	2
Lipoma	14	Fibrohistiocytoma	2
Chondroma	8	Chordoid chordoma	1
Schwannoma	7		

209 patients – 300 treatments.

therapy. Endoscopic laser resection should be the method of choice for polypoid tumors insofar as recurrence is rare if the base is well coagulated. Surgery should be reserved for cases with extraluminal growth and recurrences. Table 10 indicates the number of endoscopic laser procedures carried out for benign tumors in our series.

It should be noted that location, not cell type, is the most important factor for the outcome of laser therapy. As shown in figure 6, best results are obtained in the trachea and main stem bronchi because they are the most accessible locations to rigid bronchoscopy. These are also the locations that cause the severest impairment of ventilation. During treatment of tracheal lesions, the first priority is to establish an airway. The most expeditious way to do this is simply to push the bronchoscope slowly but forcibly through the stenosis. For bilateral lesions involving both main stem bronchi, e.g. astride the carina, it is advisable to begin on the less obstructed side in order to establish a reliable airway as soon as possible.

Laser resection in third-order bronchi poses special hazards due to poor accessibility and thinness of the walls (risk of perforation). Segmental lesions usually do not cause symptoms severe enough to warrant laser surgery, and the only indications for laser disobstruction are drainage of distal purulent secretions and cure of benign tumors. Work in the upper lobes often requires use of the fiberscope which further increases the risks. A safer technique is to use the open tube as a conduit for the fiberscope.

Another important factor in the outcome of laser resection for airway tumors is degree of extrinsic compression. Complete resection of polypoid tumors is simple. Obviously purely extrinsic compression is a contraindication for laser therapy. In cases involving tumors with both

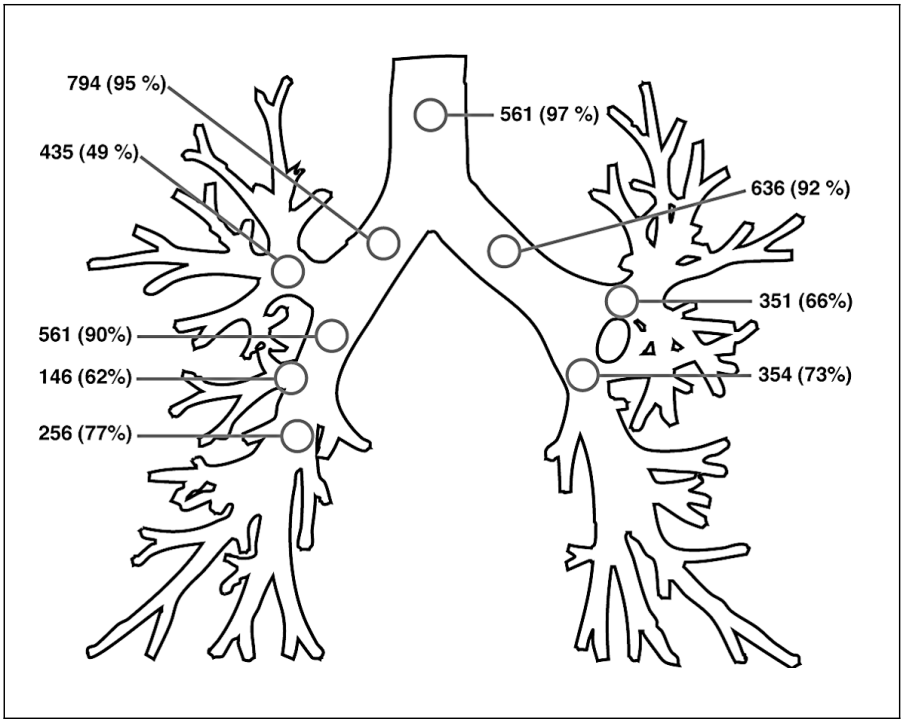

Fig. 6. Bronchogenic carcinoma. Immediate outcome of therapeutic bronchoscopy in function of location. The number of lesions in each region and corresponding percentage of satisfactory results after first treatment (in parentheses).

intraluminal and extraluminal involvement, the intraluminal component can be resected, but tumor growth generally leads to quick recurrence. In these cases stenting is necessary to ensure lasting results.

Laser resection provides immediate relief of airway obstruction and thus can be used as a bridge to chemoradiotherapy and even surgery. Combination with external beam radiotherapy or endobronchial brachytherapy is particularly useful. Laser resection should always be performed first to allow the patient to undergo radiation therapy under optimal conditions. Previous data has shown that radiotherapy and chemotherapy are poorly effective on endoluminal airway obstruction (30% good results). A detailed description of multimodality treatment of advanced tracheobronchial diseases is provided in the chapter by Bolliger.

Iatrogenic Tracheal Stenosis

Therapeutic bronchoscopy has greatly modified the approach to management of iatrogenic stenosis. In combination with medical treatment, endoscopic treatment using laser, mechanical dilatation and stenting can be highly effective. Surgery is rarely indicated as the primary therapy. Figure 7 gives an algorithm summarizing the use of therapeutic bronchoscopy for iatrogenic tracheal stenosis.

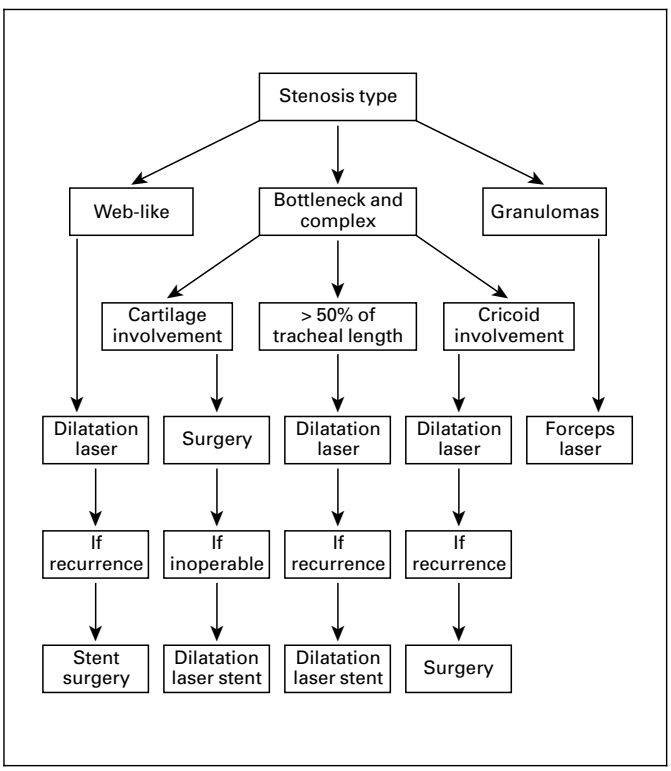

Fig. 7. Algorithm summarizing use of therapeutic bronchoscopy for management of iatrogenic tracheal stenosis.

Table 11. Iatrogenic stenoses treated by therapeutic bronchoscopy between April 1982 and March 1997 (Cavaliere)

Type of narrowing	Patients	Treatments
Granuloma	136	203
True stenosis	363	747
Total	499	950

An important factor in therapeutic decision making for iatrogenic tracheal stenosis is the type of lesion. The simplest form is granuloma due to formation of granulation tissue in the lumen. Granulomas are not true tracheal stenoses since the wall of the trachea is not involved. The second type of tracheal stenosis is the web. Webs correspond to formation of a fibrous membrane growing circumferentially from the tracheal wall towards the center of the lumen. These lesions are localized and the structure of the trachea is not altered. The third type of tracheal stenosis is bottleneck stenosis due to collapse of the tracheal wall involving a short segment of the trachea (not more than 5 cm). The fourth form of tracheal stenosis is complex stenosis which designates narrowing due to a combination of granuloma, web and/or bottleneck stenosis or to extensive lesions involving a long segment of the trachea. Table 11 shows the number of patients and treatments corresponding to iatrogenic tracheal stenosis in our experience.

The laser is useful in patients with simple lesions and in patients who are ineligible for surgery due to the length of the lesion or to associated risk factors (e.g. age and intercurrent disease). In these patients endoscopic treatment is the only alternative and should be used freely. Several other points deserve to be underlined. First, in the context of tracheal stenosis, laser resection is complementary to tracheal dilatation using progressively larger tubes. Only fibrous lesions and granulomas projecting into the lumen of the trachea can be resected. For webs, the laser should be used only at high power to make 3 or 4 radial incisions. Second, laser therapy should be used instead of tracheotomy as first-intention treatment in patients with acute dyspnea. Third, surgery and endoscopic therapy are not mutually exclusive. Surgical patients may benefit from endoscopic laser therapy to allow stabilization of the lesion. Fourth, stenting is very useful as a means of maintaining airway patency after dilatation and laser resection.

Table 12. Miscellaneous indications treated by therapeutic bronchoscopy between April 1982 and March 1997 (Cavaliere)

Miscellaneous indications	n
Bronchial granuloma	77
Hemorrhage	64
Tuberculosis-related stenosis	46
Stenosis after sleeve resection or radiation therapy	37
Bronchial fistula	23
Suture thread removal	18
Vascular dilatation	13
Wegener's granulomatosis	13
Inflammatory pseudotumors	11
Tracheopathia osteoplastica	8
Others	50

360 patients – 575 treatments.

Miscellaneous Indications

Miscellaneous indications include bronchial granuloma, hemorrhage, tuberculosis-related stenosis, bronchial fistula, suture thread removal, vascular dilatation, Wegener's granulomatosis, inflammatory pseudotumors, tracheopathia osteoplastica and foreign body removal. The number of patients and treatment for these indications are summarized in table 12.

Laser bronchoscopy has greatly improved emergency treatment of massive hemoptysis regardless of the cause. Using the rigid bronchoscope, which allows simultaneous ventilation, aspiration and treatment, it is possible to establish an airway, locate the source of bleeding and achieve hemostasis in almost all cases. An important precaution when treating hemoptysis is to turn the patient on the bleeding side in order to prevent blood from flooding the healthy contralateral lung. By continuous aspiration of blood or by injection and aspiration of adrenaline-containing saline, it is possible to locate the source of bleeding. The laser can then be used to coagulate the bleeding site.

Long-Term Results

Long-term results of therapeutic endoscopy for malignant airway tumors are difficult to interpret since TNM restaging was not performed and therapies used before and after laser treatment varied widely. In a series by Cavaliere, cumulative survival in the first 333 patients was

50% (± 3%) at 6 months and 26% (± 3%) at 1 year. This study was stopped because we consider that survival is not a suitable criterion for evaluating a modality used mainly for symptomatic/palliative relief. Other authors have reported that laser therapy extends survival, but we think the technique should be judged on the basis of immediate improvement in quality of life. In this regard it should be emphasized that good immediate results with significant improvement in airway caliber and restoration of regional ventilation were obtained in 93% of cases overall. It is also interesting to note that respiratory distress was rarely the cause of death in our patients with malignant tumors.

As stated above, endobronchial laser therapy can be curative for typical carcinoid tumors and benign tumors. Cures have also been observed in other cases including metastatic lesion of tracheobronchial mucosa, early cancers and in situ carcinomas. With follow-ups ranging from 5 to 184 months, Cavaliere [unpubl. data] observed no recurrence in the 27 patients treated for in situ carcinoma in his series.

Conclusion

Bronchoscopic laser technique has changed and improved with experience. The initial technique based purely on laser vaporization has given way to a laser-assisted technique combining laser treatment, dilatation, mechanical debulking and stenting. The laser is increasingly used primarily for coagulation before resection and in case of hemorrhage. Laser treatment of the residual tumor bed is also important after treatment to prevent recurrence. In accordance with this evolution, technological research has focused mainly on finding the most suitable wavelength for coagulation. Other advances in biomedical laser technology have involved mainly price and ergonomic features such as compactness and convenience in operation. Now as before, the goal of the therapeutic bronchoscopy is to reestablish the airway as quickly and thoroughly as possible.

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Therapeutic Bronchoscopy

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Endobronchial Electrocautery and Argon Plasma Coagulation

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Summary

Endobronchial electrocautery is the application of heat, produced by electrical current, via the bronchoscope to treat tumor tissue using a probe or a snare. Tumors located in the central airways can be treated with various bronchoscopic techniques such as lasers (Nd:YAG, Argon, KTP, CO_2), photodynamic therapy (PDT), brachytherapy, cryotherapy and electrocautery. Electrocautery is an alternative treatment technique for immediate debulking of intraluminal tumor and has a curative potential in patients with radiologically occult cancer. The various techniques of electrocautery may suit the personal experience and preference of every bronchoscopist: the rigid technique, the fiberoptic method or the noncontact mode of argon plasma coagulation. Simple logistics, relatively cheap equipment and additional instruments improve its cost-effectiveness. With recognition of the population at risk and the awareness of the potential benefit of bronchoscopic intervention in general, bronchoscopic electrocautery will increasingly become a standard part of lung cancer care.

In the majority of patients with locally advanced tumors, local control after conventional radiotherapy has been shown to be poor, ultimately leading to disease progression with local recurrence and the presence of distant metastases [1–3]. There is also a relatively high rate of second primary lung cancers after radical surgery [4, 5]. Patients who received radical treatment for a head and neck tumor are 10–40% at risk of developing a subsequent primary tumor of the lung [6].

Survival after surgery for early-stage squamous cell cancer detected by a sputum cytology screening program is close to 100% [7, 8]. In this category of patients with early stage tumor, no nodal metastases are shown if tumor thickness was <3 mm and the longitudinal tumor axis was <2 cm [9, 10].

In the last decade, technical developments have facilitated the use of endoscopic instruments for diagnostic and therapeutic purposes [11, 12]. Improved imaging and the use of smaller and more practical equipment enable bronchoscopic treatment of tumors located proximal to the segmental bronchi. Palliation and curative treatment alternatives for patients with extra- and intraluminal tumor are now available.

The purpose of this chapter is to describe the background, technique and clinical usefulness of endobronchial electrocautery. Patients with major airway obstruction require immediate relief of their symptoms by means of a simple technique. Treatment can also be applied with curative intent in treating occult, superficially spreading, intraluminal type, early stage cancer. Intraluminal bronchoscopic treatment such as photodynamic therapy (PDT) has been shown to have a curative potential, also in

patients with resectable tumor [13–15]. The issue of cost-effectiveness justifies a comparison with treatment alternatives such as electrocautery, Nd:YAG laser, cryotherapy and brychytherapy [16].

Background and History

Endobronchial electrocautery is the application of heat, produced by electrical current, via the bronchoscope to treat tumor tissue using a probe or a snare [17]. Electrocautery itself has been applied in medicine for many decades [18]. Using a high-frequency alternating current to avoid neural and muscular response, the electrical current passes through living tissue and is converted to heat because tissue resistance is high. A small probe functions as an active electrode, the heat is then focused to a tiny spot at the surface area of contact, which leads to tissue coagulation or vaporization. The degree of tissue destruction depends on the power used, duration of contact, the surface area of contact, the density and moisture of tissue. The monopolar technique is particularly suitable for endoscopic application, e.g. bronchoscopic intervention. With the monopolar technique, the electron flow current focuses toward the area of contact, which is determined by the size of the probe in contact with the tissue. The bipolar technique, in which the effect is more controllable because the electron current flows between the electrodes, is not that suitable in small hollow organs. The monopolar technique for coagulation and vaporization is widely used for endoscopic surgery such as gastroenterology and laparoscopic surgery.

Fig. 1. High-frequency electrocautery equipment (Erbotom ICC 350) with additional APC set (Erbe APC 300). The electrosurgical generator and argon gas flow are controlled by the foot switches.

Technique

The techniques of rigid and fiberoptic bronchoscopy itself will not be reviewed here. Endobronchial electrocautery can be applied either using the rigid or flexible applicator specially designed for this purpose. The most popular technique is the contact mode, in which the probe is in direct contact with tissue. The choice of technique and instruments: rigid or flexible instruments or bronchoscopes, under general or local anesthesia, depends on the expertise of the bronchoscopist and the risk assessment [19, 20].

Expertise and anticipation of possible complications during and after treatment are essential for the safety and efficacy of any bronchoscopic treatment. Patients presenting with imminent respiratory failure, hemorrhage and life-threatening airway obstruction are obviously at risk for any kind of intervention. It is therefore safer to perform this under general anesthesia to have optimal control of the situation. If immediate tumor debulking is required, any technique can be applied successfully by skilful hands. Treatment choice is more or less academic, whether this is electrocautery, Nd:YAG laser, mechanical tumor removal or a combination of these. Tumor debulking followed by stenting for extraluminal obstruction has become a standard approach [21].

The rigid electrocautery technique is comparable to the endoscopic resection technique as performed by the other specialists, such as the thoracoscopist, the laparoscopist, the urologist and the gastroenterologist. The use of a flexi-

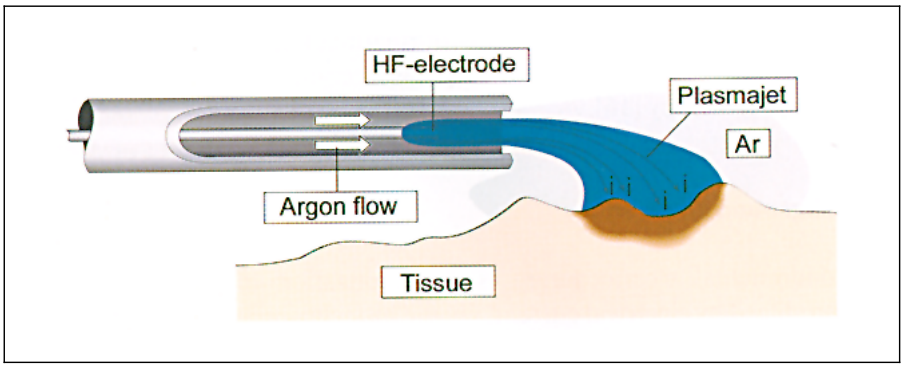

Fig. 2. Schematic representation of the flexible catheter tip for delivery of argon into the tracheobronchial tree. The argon flows around a high-frequency electrode. The argon gas (Ar) spreads out into the airway lumen, and the portion that is activated and ionized becomes the plasma jet. A spark through the plasma jet desiccates tissues (depicted by the brown area) to a specific depth.

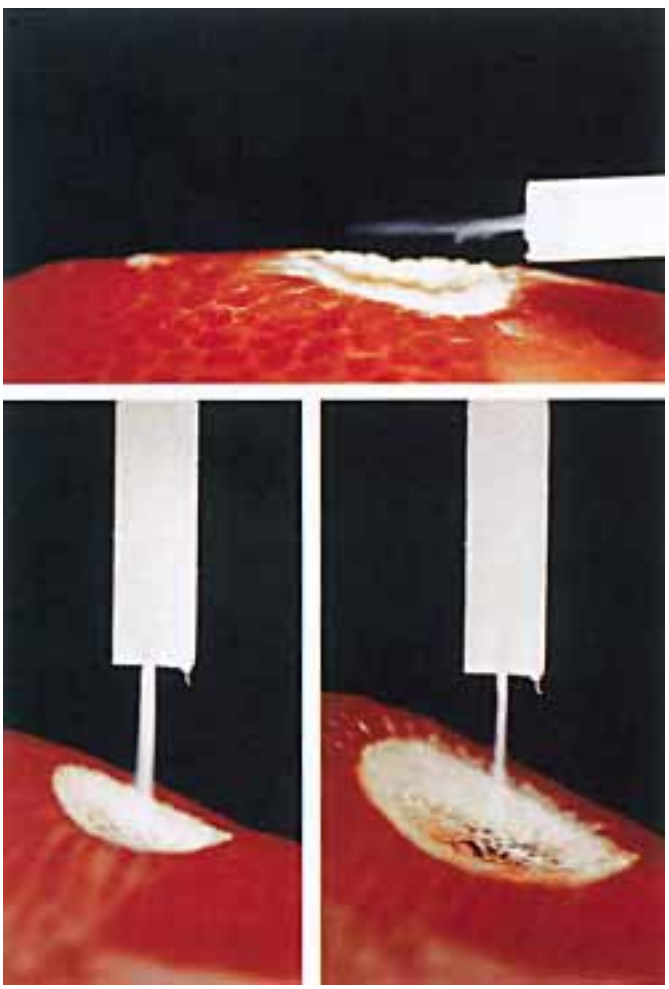

Fig. 3. Argon beamer effect illustrated on liver surface. Top: Although the beam is directed tangentially to the surface, coagulation takes place at the tissue nearest to the catheter tip. Bottom: With increasing duration of coagulation (left to right) the effect still stays superficial, but enlarges the treated area as the argon beam moves from coagulated (= high impedance) to not yet coagulated (= low impedance) tissue.

ble endoscope and an electrosurgical loop to snare pedunculated polyps is a common practice in gastroenterology. A similar technique can be applied in bronchology. Rigid bronchoscopic technique is more accepted in Europe and the fiberoptic bronchoscope is the most popular instrument in the Anglo-Saxon countries [22]. The electrocautery equipment is a standard and versatile instrument available in almost every surgical ward: e.g. Valleylab® Force Generator with Gas Surgical Unit, Erbotom® ICC 350 (fig. 1), PDS-20 Olympus.

In vivo studies showed that by using a monopolar flexible electrocautery probe, predictable but superficial coagulative necrosis by blanching the mucosa can be obtained with relative sparing of the cartilage. Under visual control during the electrocautery session, one can easily avoid charring of the bronchial mucosa to prevent too much damage and the destruction of the cartilage. The initial energy setting should be tested first on a normal part of the mucosa, before starting to treat the tumor itself. After a relatively short learning period, the bronchoscopist can have visual control and obtain a shallow necrosis of 2–3 mm without causing too much unwanted damage to the tracheobronchial wall [23]. Electrocautery is easy to learn because it is not so different from the daily practice of using the rigid or flexible biopsy forceps. Thus, electrocautery is an alternative technique for immediate tumor debulking, with the advantages of its ease, being a standard equipment and applying the familiar technique of diagnostic bronchoscopy. However, one always has to be diligent to follow the safety guidelines of bronchoscopic intervention [19].

A relatively new development is the noncontact mode of argon beam coagulation or argon plasma coagulation (APC) in obtaining superficial homogeneous tissue coagulation (fig. 2). This may be attractive for the treatment of hemorrhagic superficial spreading tumors [24, 25]. Ion-

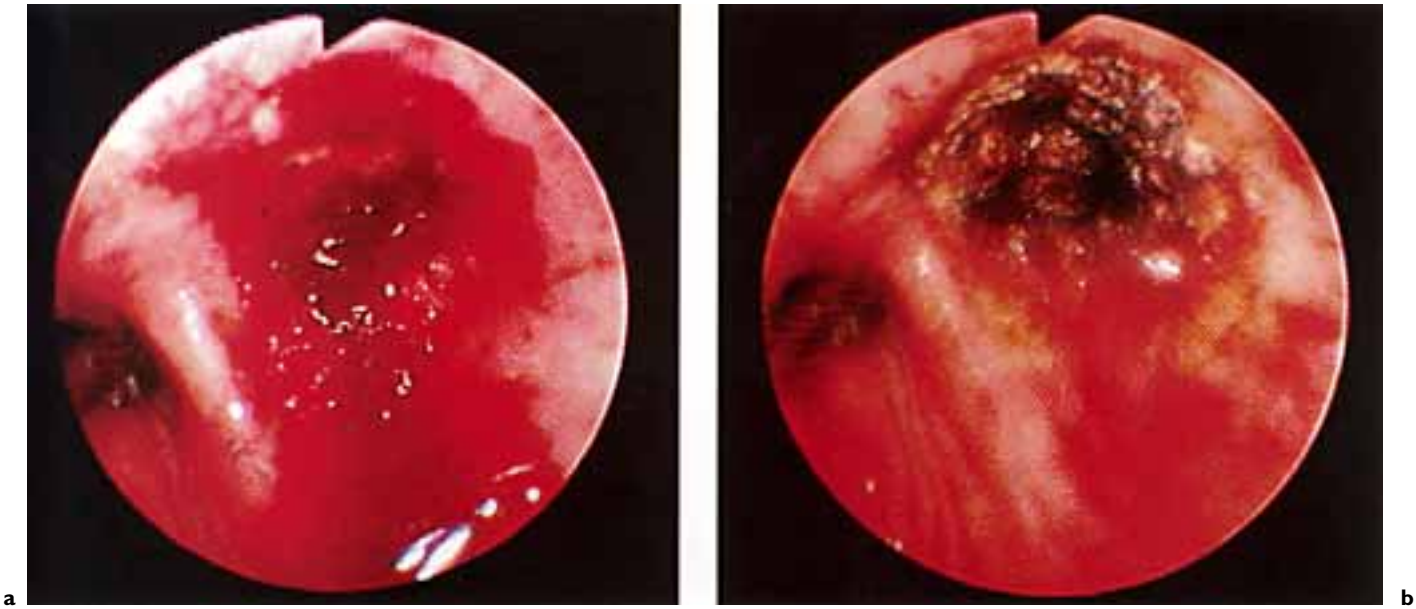

Fig. 4. Profusely bleeding tumor of left upper lobe (**a**) and perfect hemostasis with superficial carbonization after 10–15 s APC application through the flexible fiberscope (**b**).

ized argon gas functions as a conductance in the strong electrical field between the active electrode and tissue. The nearest area of contact is not necessarily straight forward from the direction of the electrode, which makes this technique suitable for treating tumors 'around the corner' at a sharp angle sideways from the tip of the electrode (fig. 3). APC has been shown to be effective in the treatment of small malignant gastrointestinal tumors [26]. Histological studies have shown coagulative necrosis to be similar either using standard electrocautery or the APC method [24–27], but APC causes more acute superficial tissue destruction and is most effective for the management of hemostasis. This superficial action makes APC a very safe tool. On the other hand, APC is less efficient than standard monopolar electrocautery or laser resection for in-depth tissue destruction of bulky tumor. Although there are reports on successful APC application in obstructing lesions of the central airways due to recurrent respiratory papillomatosis [28] or advanced bronchogenic carcinoma [29], we use APC for quick hemostasis (fig. 4) and coagulation of superficial lesions during flexible bronchoscopy under local anesthesia only. For the destruction of bulky lesions either through the flexible or the rigid scope the Nd:YAG laser or standard electrocautery are the preferred tools with immediate effect.

The Rigid Technique

Rigid bronchoscopy under general anesthesia must be considered if the bronchoscopist feels that optimal control is required during the session. It is safer and less time-consuming to use the rigid scope [20]. This allows adequate ventilation and rapid tumor debulking in patients with imminent respiratory failure caused by hemorrhagic bulky tumor. Obviously, tissue coagulation can be achieved by using the rigid probe in combination with the flexible instruments to improve maneuverability. Thereafter, tumor debulking can be carried out [19].

From a mechanical and physical point of view, electrocautery technique is quite similar to the contact mode of Nd:YAG laser. Tissue blanching and charring is immediately apparent, so the applied energy can be adjusted any time. Comparable to the Nd:YAG laser technique, coagulated tissue can be sheared off the wall mechanically using the bevel of the rigid scope, the biopsy forceps or the fiberscope shaft [19]. The process of coagulation and debulking can be repeated until sufficient airway passage has been obtained. In contrast to the Nd:YAG laser, electrocautery achieves superficial necrosis, as electrons do not scatter in comparison to the laser photons of the Nd:YAG laser. Also, current leak may occur during electrocautery treatment, and it is important to keep the treated area dry, free of mucus and blood [17, 18]. Conse-

Fig. 5. The rigid loop and the rigid suction probe for monopolar electrocautery. Enlarged view of the distal tips of the instruments. From [72].

Fig. 6. The insulated fiberoptic bronchoscope and the flexible monopolar probe for contact electrocautery; alongside the bronchoscope is an electrosurgical snare.

quently, a stent can be inserted if residual extraluminal stenosis becomes apparent.

The rigid technique of electrocautery is usually performed under general anesthesia. After induction of anesthesia, the rigid scope is introduced and ventilation maintained by jet ventilation. For rigid electrocautery probes, one can use the Storz® high-frequency loop electrode 10440 A or the rigid coagulation suction probe 10390 N (fig. 5). Intraluminal tumor mass is gently stripped or coagulated with the coagulation probe. Energy of about 50 W is applied by activating the electrical current using the foot switch. Continuous suction of mucus, debris and blood while performing coagulation is necessary to avoid current leak. The probe can be used to palpate the tracheobronchial wall to feel the anatomical rigidity and to assess the compliance of the tracheobronchial wall. If the choice had been local anesthesia, it is sensible to anticipate possible complications by having an intravenous line for giving sedatives [30]. Two milligrams midazolam are injected as a bolus via the intrave-

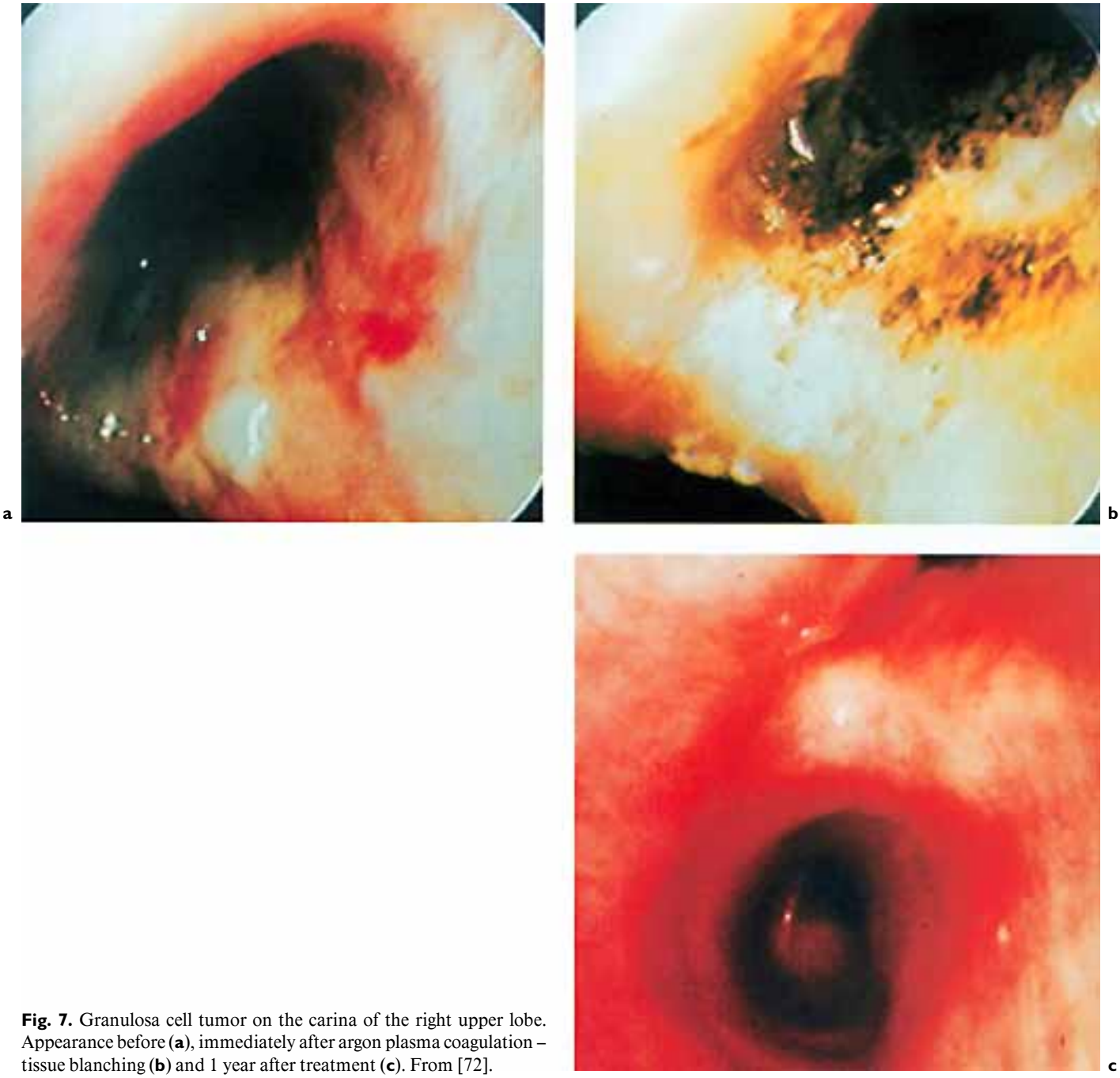

Fig. 7. Granulosa cell tumor on the carina of the right upper lobe. Appearance before (**a**), immediately after argon plasma coagulation – tissue blanching (**b**) and 1 year after treatment (**c**). From [72].

nous line, immediately before starting the procedure. Additional midazolam can be titrated during the session by dripping infusion. The session is done under trend monitoring by pulse oximetry and by giving supplemental oxygen. The bronchoscopist has to be able to immediately intubate or insert a rigid scope in case of an emergency. We always keep the rigid scope ready for use at all times. The rigid scope can be mounted with two cuffs mimicking a Carlens tube to enable adequate ventilation while continuing treatment.

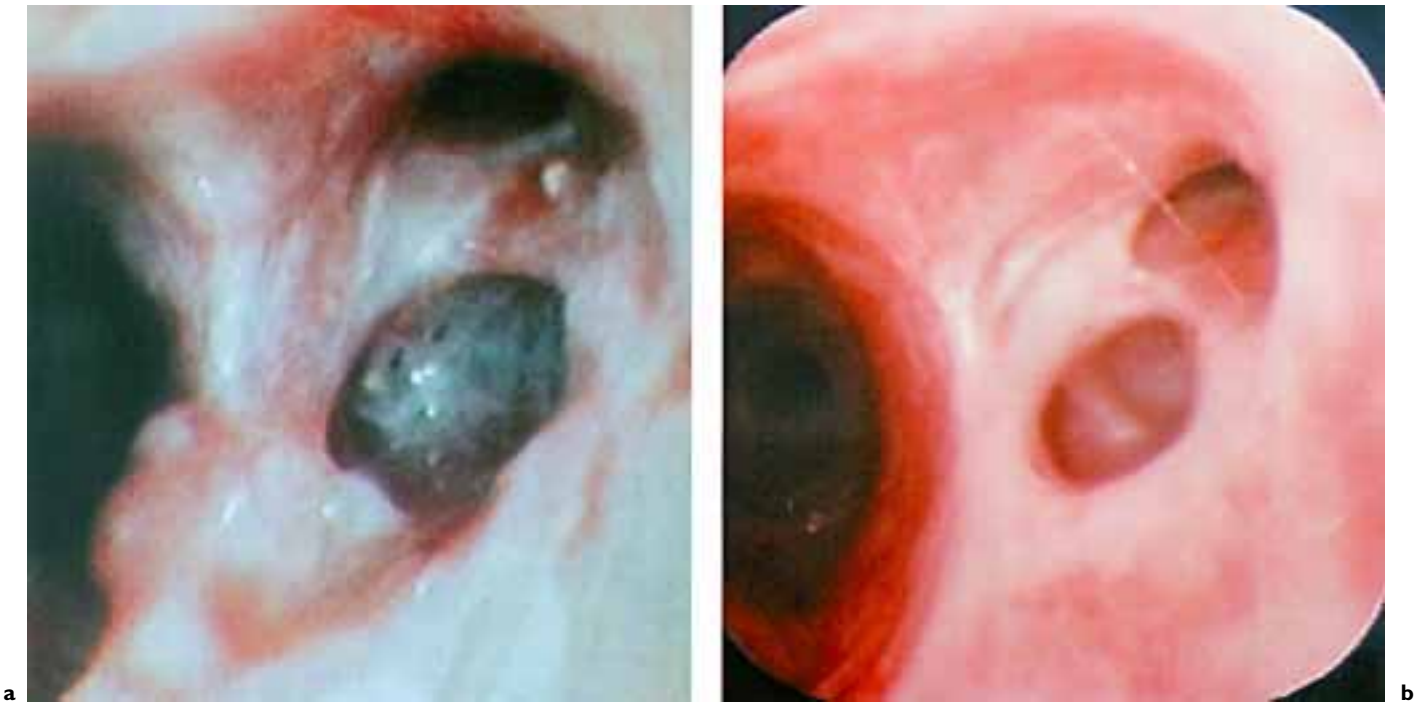

Fig. 8. Microinvasive early-stage carcinoma, before (**a**) and 6 weeks after (**b**) monopolar electrocautery treatment with curative intent in roentgenologically occult lung cancer as an alternative to photodynamic therapy and surgical resection. From [72].

The Flexible Technique

The flexible technique allows a better reach of smaller-size tumors located in the bronchial segments. An insulated fiberscope (Olympus®; fig. 6) theoretically is safer in preventing current leak [18], allows a better control of the process of coagulation and avoids burns or electrical shock to both the patient and the bronchoscopist. The tumor area should be kept free of blood or mucus by continuous suctioning. Coagulation can be achieved by gently touching the tumor base along the bronchial wall, applying 20–40 W until sufficient blanching of the mucosa becomes apparent. One can easily watch the effect of electrocautery on the treated area. The noncontact method of APC is another alternative. It is comparable to the noncontact mode of CO_2 laser that can be used to spray the tumor area to obtain superficial hemostasis, with the advantage of treating areas from an angulated position where the probe is located without any difficulty. Electrons will follow the path of the least conductance, where the flows then will diverge toward the plate placed on the patient's skin. Tissue blanching can be achieved in a matter of seconds, both with standard monopolar electrocautery (fig. 7) and APC (fig. 8), having the advantage of being able to treat tumors obliquely if one cannot make the tight bend using the fiberoptic bronchoscope. Treatment duration is very short if tumors are superficial and the surface area is limited to a few square centimeters and can certainly be performed under local anesthesia. It is of the utmost importance, however, to first consider the real indication and the oncological limitations of treatment with curative intent in patients with early-stage cancer [9, 10, 12], especially in those with resectable malignancies.

Palliative Treatment

Results of electrocautery for palliation are shown in table 1 (the rigid technique) and in table 2 (the flexible technique) [31–40]. The results show that electrocautery is equally effective in achieving tumor coagulation and debulking compared to Nd:YAG laser and the complication rate was not excessive. It is not surprising that comparable results are seen in comparison to other debulking techniques, as the purpose of all these is mainly tumor

Table 1. Palliative results of endobronchial electrocautery using the rigid loop bronchoscope [from ref. 72]

Ref.	n	Technique	Response	Complications
Ledingham and Goldstraw [31]	15	general anesthesia, rigid loop + radioactive grains	successful palliation, 11/15 alive >1 month; median 2.5 months	no
Pedersen et al. [32]	10	general anesthesia, jet ventilation and rigid loop	palliative 3–14 months, adenocystic 2–29 years	no
Petrou et al. [33]	29	general anesthesia and rigid loop (+ stents, + radioactive grains)	19/20 improved symptoms	no

Table 2. Palliative results of endobronchial electrocautery using the fiberoptic bronchoscope

Ref.	n	Technique	Response	Complications
Frizelly [34]	17	GA/LA, FFB	average palliation 4–5 months (9 months)	1 hemorrhage
Hooper and Jackson [35]	4	GA, FFB + snare	all successful	1 fire/explosion + respir. failure
Hooper and Jackson [36]	18	GA/LA, FFB + snare + bipolar probe	5 benign successful 13 palliation follow-up 3 years	1 bleeding and 1 fire
Gerasin and Shafirovsky [37]	14	GA, FFB + snare	10/14 complete and 2/14 >75% clearance	1 bleeding (100 ml) 2 emergencies for bleeding/suffocation
Sutedja et al. [38]	17	LA and FFB + probe	15/17 successful 2 extraluminal	1 minor bleeding 1 pneumonia
Homasson et al. [39]	32	LA, rigid and flexible	27/32 >50% tumor reduction, 11/12 hemostasis	2 bleeding
Sutedja et al. [40]	56	GA/LA, mostly FFB + probe	39/56 (70%) remaining extraluminal tumor	1 bleeding

GA/LA = General/local anesthesia; FFB = flexible fiberoptic bronchoscope. From [72].

coagulation to reduce the chance of hemorrhage before the tumor is mechanically removed. So, treatment results of all phase II studies strongly depend on the patient population or selection and the expertise of the bronchoscopist.

Treatment with Curative Intent

Early-stage lung cancer is a rarity and usually detected by chance, either as a synchronous tumor or as a metachronous subsequent primary tumor. Particularly at risk are those who have had a previous malignancy of the upper respiratory tract [6]. Early-stage cancer lesions are easily missed by conventional bronchoscopy [41]. The number of patients with early-stage lung cancer treated bronchoscopically with curative intent is small, and experience in using electrocautery is very limited. Many patients with occult cancer who are regarded as inoperable because of poor pulmonary function, have already undergone previous treatment with curative intent. The majority of them have been treated with PDT [13–15]. The preference for PDT in using hematoporphyrin derivatives as sensitizers was based on the theory of 'selective' damage with relative sparing of normal tissue. However, clinical data do not support this theoretical background. The fact is that tumor area is selectively illuminated, and drug selectivity is a controversial issue [42, 43]. Cicatricial fibrosis due to treatment-induced hyperthermia may occur [44], and normal tissue, if illuminated, may also be damaged [45].

Any kind of bronchoscopic technique is potentially curative for occult, superficial and intraluminal lung cancer [12]. Occult tumors only several millimeters thick with <3 mm invasion of the bronchial mucosa and visible distal margin can be effectively treated bronchoscopical-

ly, as an alternative for surgical resection [9, 10, 14, 15]. These oncological considerations are far more important arguments than the issue of the proper treatment technique. Hence, the results of bronchoscopic treatment with curative intent strongly depend on the inclusion criteria of these early-stage lesions or the exact staging, showing a strong correlation between complete response rate and tumor size [13]. A small number of patients with superficial spreading squamous cell cancer may also be treated prior to surgery, to free the proximal tumor margin before resection, thus improving the chance for radical surgery by using PDT, Nd:YAG laser and brachytherapy [46–48]. This is an approach that can be applied in patients with severe COPD in whom a less extensive surgical resection may still offer the best chance for cure. Also, patients with low-grade malignant tumors such as intraluminal typical carcinoid may be treated bronchoscopically with curative intent [49–51]. Again, the oncological considerations of tumor histology and type are far more important than the technique of bronchoscopic intervention. Surgery is a relatively wasteful technique of lung parenchyma resection in these early-stage cancers, justifying alternatives to be applied with curative intent (table 3). Without doubt, in carefully selected cases, a bronchoscopic treatment is a worthy consideration instead of a radical surgical resection.

A phase III randomized study versus surgical resection in patients with occult cancer is difficult to perform due to the low number of patients that can be included in such a study [14, 15, 52]. Detection of early-stage lung cancer is mostly a chance occurrence. Any technique seems to be justified in treating a tumor several millimeters thick, as long as staging is oncologically correct. Inaccurate assessment of tumor dimension is the real hurdle in lung cancer management, and the true tumor stage can only be definite in retrospect, after surgical resection with complete

Table 3. Results of bronchoscopic intervention for roentgenologically occult cancer

A Photodynamic therapy with curative intent

Ref.	Lesions	Response	Survival months
Cortese and Edell [52]	23	CR 9/12 (43%, resectable candidates!)	21–116
Furuse et al. [53]	59	CR 45/59 (83%)	14–32
Okunaka et al. [54]	10 synchronous	10/10 synchronous (100%)	14–87
	17 metachronous	16/17 metachronous (94%)	
Sutedja et al. [55]	39	CR 28/39 (72%)	2–95

B Other techniques

Ref.	n	Technique	Survival
Brachytherapy treatment with curative intent			
Macha and Wahlers [56]	9	15 Gy at 3 mm/4 × HDR	<27 months
O'Driscoll et al. [57]	6	15–20 Gy/1 × HDR	12–21 months
Hernandez and Donath [58]	4	7.5 Gy/? HDR	8–24 months
Sutedja et al. [59]	2	10 Gy/2–3 × HDR	25, 54 months
Ono et al. [60]	12	50–60 Gy	2–8 months
Electrocautery for occult cancer and typical intraluminal carcinoid			
van Boxem et al. [61]	12/15 (80%)	LA with flexible probe	16–43 months
van Boxem et al. [50]	14/19 (73%)	GA with flexible probe, resectable patients!	16–43 months
Nd:YAG laser for occult cancer and intraluminal carcinoid			
Cavaliere et al. [62]	19 ca. in situ	GA, rigid bronchoscope	<12 years
Personne et al. [63]	3/30 carcinoids	GA, rigid bronchoscope	2–4 years

CR = Complete response with negative histology/cytology; HDR = high-dose-rate brachytherapy; GA/LA = general/local anesthesia. Modified from [72].

lymph node dissection. The improvement of our diagnostic accuracy in assessing peribronchial, nodal and distant metastasis should also be the focus of our attention in bronchoscopic techniques. High-resolution CT, ultrasonography, fluorescence bronchoscopy are worth to be investigated to improve the staging in lung cancer screening programmes.

Electrocautery and Other Treatment Modalities

Are treatment modalities such as mechanical removal [64], PDT, Nd:YAG laser, cryotherapy [65] and brachytherapy comparable to electrocautery? Each technique has its own merits and limitations. Treatment choice is usually based upon various factors: clinical presentation, the expertise of the bronchoscopist, anesthetic care and the technical facilities of each hospital. Practical aspects, such as logistics and cost, may further influence treatment choice. Many patients have imminent respiratory failure because of bulky tumor in the intra- and extraluminal compartment. Immediate tumor debulking may be required using Nd:YAG laser, electrocautery and mechanical removal, and a stent can be inserted for extraluminal stenosis [21]. In nonemergency cases, brachytherapy is a good alterantive to obtain durable response at the cost of normal tissue damage. About a 10% complication rate, e.g. radiation bronchitis, radiation stenosis, fistula and hemorrhages, is reported after high-dose-rate brachytherapy [66]. Costs and comparison between the different techniques are shown in tables 4 and 5. An algorithm for palliative endoscopic and nonendoscopic treatment options is presented in the chapter on multimodality treatment of advanced pulmonary malignancies by Bolliger.

Electrocautery is a cheaper alternative than Nd:YAG laser for tumor coagulation. The cost-effectiveness of any technique also depends on the price of the equipment, maintenance costs and its use by the different specialists. Electrocautery is a simple and straightforward technique that can be used by the different specialists in a hospital. In our daily practice, the majority of patients are treated for local palliation and treatment choice is also based on logistics, thus based on pragmatism.

Table 4. Treatment costs of bronchoscopic intervention in The Netherlands (calculated in USD)

	Price of equipment	Cost refund[1]
Bronchoscopy		309
Anesthesia		318
Nd:YAG laser, diode laser	40,000	880
Photodynamic therapy, diode laser	60,000	3,077[2]
Brachytherapy (high dose rate)	250,000	539
Electrocautery	20,000	309

[1] Based on tariffs of the 'COTG' (Government Health Insurance Tariff).
[2] Photofrin II drugs as sensitizers, 2 mg/kg, on average 2 vials are needed.
Modified from [72].

Table 5. Advantages and disadvantages of various bronchoscopic intervention techniques

Treatment	Equipment/technique	Result	Complications
Mechanical removal	standard, GA	short-term, immediate	bleeding
Cryotherapy	special applicators and mostly GA	not immediate, save for the cartilage	secondary necrosis
Electrocautery	standard, GA/LA, rigid and fiberscope	immediate and superficial	fibrosis
Nd:YAG laser	laser, mostly GA, or fiber through rigid	immediate and in-depth effect	perforation
Brachytherapy	afterloading, LA	late and in-depth effect	radiation bronchitis, stenosis, fistula
Photodynamic therapy	dye and diode laser, LA	save the cartilage, secondary but in-depth effect	skin photosensitivity, secondary necrosis

GA/LA = General/local anesthesia. Modified from [72].

Conclusion

Tumors located in the central airways can be treated with various bronchoscopic techniques such as lasers (Nd:YAG, Argon, KTP, CO_2), PDT, brachytherapy, cryotherapy and electrocautery. Stenting is necessary for extraluminal airway stenosis. Thus, various techniques can currently be applied safely and effectively to treat patients with malignancies in the major airways, both for immediate palliation and for treatment with curative intent. Usually, bronchoscopists have to deal with bulky tumor, in which the visible intraluminal tumor is only the tip of an iceberg. Improvement of gas exchange is the aim of airways reopening, but regions with low gas exchange, e.g. after external irradiation, may improve little if treated. Obstructive pneumonia and hemoptysis are good palliative indications. Patients' general, cardiac and pulmonary condition, tumor dimension and stage, bronchoscopic findings, (high resolution) CT findings and regional ventilation-perfusion are factors to be taken into account prior to any intervention. Risk and potential benefit also depend on the expertise of the bronchoscopist and the available facilities in each institution.

Results are immediate when using electrocautery or lasers (Nd:YAG, KTP, Argon, CO_2) in combination with mechanical tumor removal. Techniques that induce late response or cause secondary necrosis, e.g. brachytherapy, PDT and cryotherapy, are less practical for emergency cases. PDT and brachytherapy can obtain an in-depth effect, the latter at the cost of normal tissue damage. Secondary necrosis and fibrin plugs may require additional bronchoscopy for nectrotomy (cryosurgery, PDT) and skin photosensitivity in PDT may increase treatment morbidity.

A small number of patients with intraluminal occult lung cancer may benefit from bronchoscopic treatment with curative intent. Treatment may also be used to improve resectability. However, occult tumors with full thickness invasion of the bronchial mucosa and invisible distal margin are unlikely to be cured by bronchoscopic treatment alone. One should always keep in mind the oncological limitations in bronchoscopic intervention. In patients with resectable tumors, staging inaccuracy is the most important factor, not the treatment technique. High-resolution computed tomography [67], fluorescence bronchoscopy [68, 69] and bronchoscopic ultrasound [60, 70] may improve our ability to improve tumor staging procedures.

A simple and cheap bronchoscopic technique such as electrocautery improves the cost-effectiveness of a bronchoscopic intervention, especially when more complicated and expensive procedures have not been shown to be clinically superior. Electrocautery proves also to be effective in treating benign and low-grade malignant lesions such as intraluminal typical bronchial carcinoid. The curative potential of various bronchoscopic therapies provide us with alternatives for surgical resection in treating early-stage lung cancer lesions or relatively benign tumors which are amenable for surgical bronchoplasty. With the recognition of the population at risk and the awareness of the potential benefit of lung cancer screening [71], techniques such as electrocautery will become part of standard lung cancer care.

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Cryotherapy for Endobronchial Disorders

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Summary

Cryotherapy has been used for destruction of endobronchial tumors. Cryotherapy works by its cytotoxic effect, by freezing the tissue, thus causing tissue death. Cryotherapy can be performed by rigid bronchoscopy under general anesthesia. It can also be performed by fiberoptic bronchoscopy under sedation and local anesthesia. The indications for cryotherapy are similar to those for endobronchial laser or electrocautery. The purpose of cryotherapy is essentially to ablate the endobronchial tumor. Cryotherapy has also been used for treatment of carcinoma in situ as well as benign endobronchial tumors. The advantages which cryotherapy provides is safety not only for the operator, but also for the patient. The major counterindication for cryotherapy is a patient with impending respiratory failure. In certain situations cryotherapy has also shown to have a beneficial effect in conjunction with radiation therapy as well as chemotherapy. Cryotherapy offers an alternative for endobronchial tumor ablation with significant safety as well as being relatively inexpensive.

History of Cryosurgery

Documents from 3500 BC described the use of cold as treatment for swelling and war wounds [1]. Hippocrates described the use of cold to treat orthopedic injuries [1]. The analgesic and anti-inflammatory properties of ice have been known for several centuries, but the use of freezing as a therapeutic agent for destruction of tissue began in 1845–1851. Arnott [2, 3] described the use of salt solutions containing crushed ice at a temperature of about −8 to −12 °C to freeze advanced cancers in accessible sites, producing reduction in tumor size and improvement of pain. The Joule-Thomson effect, which is the sudden expansion of a gas from a high- to a low-pressure region, is the basis for the functioning of some cryoprobes, especially in pulmonary medicine. White [4, 5] showed that liquid air could be used for the treatment of various dermatological lesions. Hass and Taylor [6] described freezing local lesions in several organs; necrotic lesions were sharply defined uniformly with a lack of suppuration or sequestration and were accompanied by a slow healing process.

During the next several years, many cryosurgical machines were developed in most medical specialties [7–17]. Due to the relative inaccessibility of endobronchial lesions, cryosurgical techniques were late to develop. The destructive effect of cold has also been confirmed by the healing of the tracheobronchial tree, with the restoration of a normal ciliated epithelium without stenosis in mongrel dogs [18–24]. The first patient who had a carcinomatous obstruction of a bronchus was treated in 1968, and Sanderson et al. [25] reported another case in 1975. This first study by the Mayo Clinic included 28 patients with endobronchial tumors, and the investigators concluded

Table 1. Cryosensitive and cryoresistant tissues

Cryosensitive	Cryoresistant
Skin	Fat
Mucous membrane	Cartilage
Nerve	Nerve sheath
Endothelium	Connective tissue
Granulation tissue	Fibrosis

that cryotherapy did serve as a good alternative for palliation. In Europe, Homasson et al. [26] rediscovered cryotherapy in France, Maiwand [27] in England and Astesiano et al. [28] in Italy. Since the early 1980s, most of the work with endobronchial cryotherapy has occurred outside the US, where the introduction of laser diminished interest in cryotherapy. In 1994, a flexible cryoprobe (ERBE USA Inc., Marietta, Ga., USA) for use with the flexible bronchoscope was introduced in the US renewing interest in endobronchial cryotherapy. In 1996, Mathur et al. [29] described the use of this probe with the flexible bronchoscope in treating 22 patients with airway obstruction. During the decade 1985–1995, cryosurgery has undergone a renaissance, and different specialties are using this technique, such as pulmonology, dermatology, urology and liver metastasis surgery. The literature has shown the efficacy of cryosurgery [29–41] and its association with other treatment modalities such as irradiation [42] or chemotherapy [43]. It is a cytotoxic procedure and as such should be integrated into the plan of action of treatments for bronchial carcinomas.

Scientific Basis of Cryosurgery

Cryotherapy deals with the destruction of biological materials through the cytotoxic effects of freezing. There has also been a parallel development in the subject of cryopreservation, which deals with attempts to use freezing for the long-term preservation of biological materials. The fundamental processes that occur during cryosurgery derived from research done on the use of freezing to preserve biological cells or tissues. Understanding the process of freezing and the mechanisms of damage is very important. One key to the success is having a clear understanding of the impacts that low and changing temperatures have on cell and tissue structure.

The damage induced by freezing occurs at several levels, including the molecular level, the cellular level, structural level and the whole tissue. The effect of a freezing injury is influenced by many factors, and the survival of cells is dependent on the cooling rate [44–46], the thawing rate [47], the lowest temperature achieved [48] and repeated freezing-thawing cycles [49, 50]. Certain tissues (table 1) are cryosensitive (skin, mucous membrane, granulation tissue), and others are cryoresistant such as fat, cartilage, fibrous or connective tissue. The cryosensitivity depends on the water content of the cells. Tumor cells may be more sensitive than normal cells [50].

Mechanisms of Cellular Damage by Freezing

The physical events occurring in cells in suspension during freezing, are as follows [50]: (1) At –5°C, the system remains in a liquid state, despite the cytoplasmic freezing point of –2.2°C. (2) Between –5 and –15°C, extracellular crystals form while the intracellular medium remains supercooled and unfrozen as the cell membrane is a barrier to the propagation of ice. It is at this stage that the rate of cooling determines the outcome. If the cell is cooled slowly enough, the dehydration of intracellular water allows the buildup of an intracellular solute concentration that eliminates any intracellular freezing. However, if the cell is cooled too rapidly, the intracellular water will not have enough time to pass the cell membrane before crystals form within the cell. (3) Below –15°C, a transitional state occurs, after which any further increase in solute concentration results in a decrease in the freezing point. (4) Finally, the solid state or complete crystallization is attained.

During thawing, different physiochemical phenomena occur which again are determined by the cooling velocity: (1) after a suboptimal freezing, rapid thawing exposes the cell to a high electrolytic concentration and to an elevated temperature, which could induce an intra- or extracellular recrystallization; (2) after supraoptimal freezing, slow thawing induces the recrystallization phenomenon; this is an extremely destructive process for intracellular organelles due to the grinding action of ice [51, 52]. During this physical period, factors involved in the determination of cellular cryolesion and cell death are: extracellular crystallization that compresses and deforms the cells ('pack-ice effect'), intracellular crystallization, cellular dehydration with collapse, increases in intracellular electrolytic concentration, denaturation of membranous lipoprotein and simple thermic shock.

These factors are closely related and intervene to different degrees in the determination of cellular cryolesions.

Both mechanical effects due to the formation of ice crystal and more complex biochemical effects secondary to cellular dehydration occur. Nevertheless, the essential determinant of the final degree of cellular lesion is the cooling velocity. The study of these factors provides the basis of the following advice to cryosurgeons; the aim of using low-temperature instruments is to create the fastest possible freezing of the target tissue to provoke intracellular freezing.

Freezing of Tissue

The process of freezing depends on the details of the interaction between ice crystals, the solution surrounding the ice crystals and the cells. Tissue sensitivity to cold is dependent upon the existence of microcirculation. A clear line of demarcation between tissue that was previously frozen and tissue that was not frozen is observed after cryosurgery [53]. Following cryosurgery, the cells in the frozen region have a disrupted structure. Ischemic and infarcted aspects of cryolesions appear from a few minutes to several hours (fig. 1). Circulation stops rapidly after thawing, and this cryo-induced thrombosis seems to result from the conglomeration of several factors: (1) vasoconstriction of arterioles and venules occurring during slight hypothermia, (2) modification of the vascular endothelium, (3) an increase in the permeability of the vascular walls, (4) an increase in the blood viscosity, (5) a lowering of the intracapillary hydrostatic pressure, a decrease in blood flow and finally formation of platelet plugs. These vascular effects explain the hemostatic effect of cryosurgery, which is not always immediate. At the edge of the frozen region, hypothermia causes a heterogeneous effect and it is in these areas that chemotherapy (or radiotherapy) has a complementary destructive effect [41, 54, 55].

Ischemic damage occurs in the whole region that was frozen. The result of these cellular changes in the days following cryotherapy is cellular necrosis. An acidophilic slough forms and tumor tissue is no longer visible and therefore destroyed. Nevertheless, freezing does not modify histopathological findings when biopsies are made immediately after cryosurgery. The cryolesions are visible only under an electron microscope. The mechanism of cell and tissue damage after cryosurgery explains the delayed effect of this technique; the consequence is that cryosurgery is not useful for acute respiratory distress. Besides these physical and vascular effects of cryosurgery, the literature contains many references to a repeated cryoimmunologic action [56, 57]. Nevertheless, no definite conclusion is yet possible but further studies of this

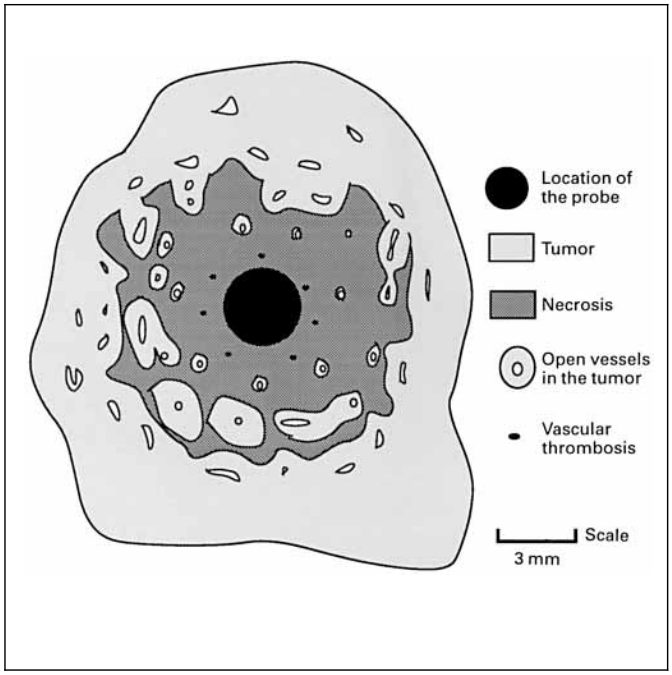


Fig. 1. Schematic view of cryonecrosis obtained after three cycles of cryotherapy applied in a single point with a rigid probe of 3 mm in diameter.

phenomenon are needed. The goal of cryotherapy is to destroy pathologic but spare normal tissue. Mazur [58] demonstrated that rapid freezing and slow warming lead to maximum cell death. Sufficient time to reach and to sustain the critical temperature is required. A large contact area between the cryoprobe and the tissue will increase the tissue mass exposed to freezing, and repeating the cycle increases the amount of destruction. In a nonhomogeneous tissue, reheated by vascularization, cold waves move radially around the point of application. At each point, the cytodestructive effect varies according to the speed of freezing and thawing.

Cytotoxicity decreases with distance from the center of application as well as near the permeable vessels. This first physical and cellular phenomenon is coupled with a vascular effect: at first, coldness induces vasoconstriction, useful to perform biopsies on well-vascularized tissues. In a second phase, vasodilatation occurs followed by microthrombosis of vessels. A complete vascular thrombosis appears 6–12 h after cryotherapy, thus completing the physical cytodestruction by local infarction. In fact, the inhomogeneous structure of the tumor determines several types of cryolesion. In the central part of the cryolesion (about 3 mm of radius around the cryoprobe) all cells are

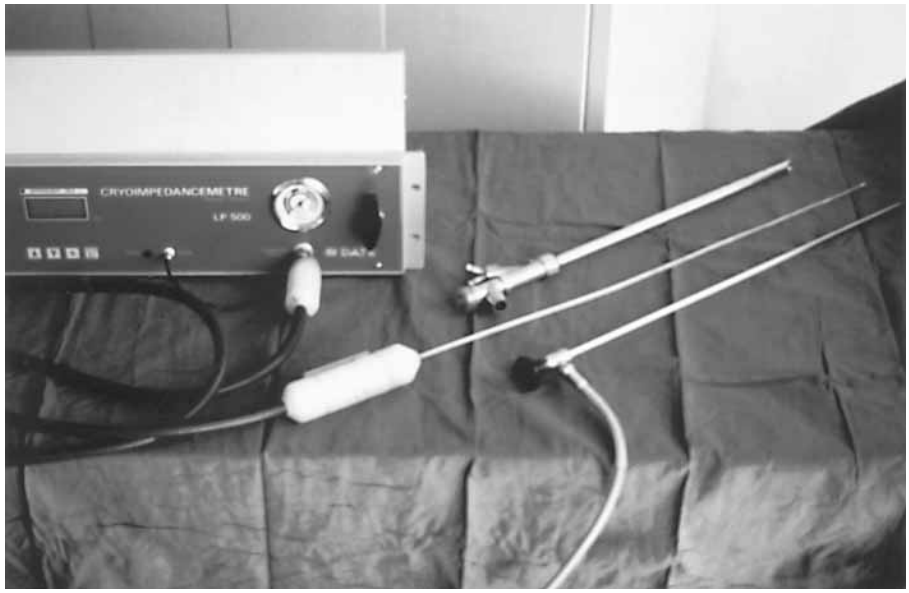


Fig. 2. French equipment (DATE) with a 'rigid' cryoprobe, the impedance meter close to the rigid bronchoscope.

destroyed with vessel of thrombosis. Then, around this area, on 3–4 mm of thickness, the cryodestruction is inhomogeneous, sparing vessels and perivascular cells (fig. 1). Nonhemorrhagic necrosis of the tissue occurs 8–15 days following the procedure. Collagen, cartilage or poorly vascularized tissues are very cryoresistant.

These data explain the essential characteristics of cryotherapy: a sphere-like volumic action, a pure cytotoxic action leading to late tissue necrosis and an important late hemostatic effect. The high resistance to cold of the supporting bronchial structure explains the safe application of this method. There is no risk of bronchial perforation nor scarring with residual fibrous stenosis.

Rubinsky showed that laryngeal epidermoid carcinoma cells are more cryosensitive than human skin with in vitro experiments using cell suspensions [22]. Several investigators have used dog models to study the effects of cryotherapy on tracheal and bronchial mucosa. In general, they have shown that the microscopic epithelial and cartilaginous changes resolve over 4–6 weeks, but the airway mucosa appears normal macroscopically by 2 weeks [25–33]. No stenoses, malacia or airway perforations occurred, supporting the safety of cryotherapy in the airway.

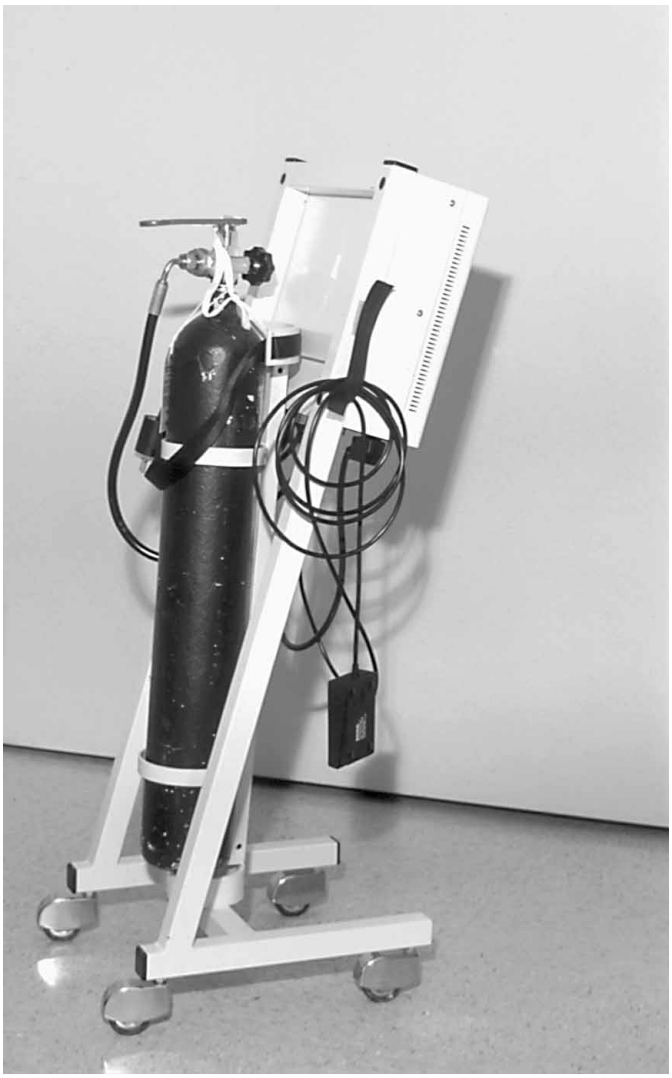
Finally, the effects of cryotherapy on the immunologic system – that is, any tumoricidal effects separate from direct injury – are not well elucidated. Some studies involving prostate carcinoma or melanoma showed increased activated peripheral lymphocytes, while others have shown the resolution of metastasis when cryotherapy was applied to the primary tumor [56, 57, 59].

Equipment

Cooling Agents

Several cooling agents can be used as cryogen. These are generally used in the liquid phase, so that on vaporization they remove heat at a constant temperature. Several studies have shown that the core temperature needed for a lesion to be destroyed is between –20 and –40°C which will cause more than 90% cell death. The choice of an effective cryogen for cryodestruction is important as the effect of treatment is directly related to the temperature achieved at the site. The two cryogens available to the pulmonologist are (1) liquid nitrogen (LN_2) and (2) nitrous oxide (N_2O).

LN_2 is easily obtainable, and is stored near its saturation temperature (–196°C) in a vacuum insulated container to reduce the loss of liquid by evaporation. As LN_2 passes through the cryoprobe at room temperature, it evaporates, and the gas in contact with the metal tip results in slow cooling of the tip (with bronchial cryoprobes, the temperature of –196°C is reached in about 1 min for the first freeze/thaw cycle and more rapidly, in 20–30 s, for the other cycles).



3

4

Fig. 3. Three probes manufactured by ERBE are available in the US – flexible, semirigid, and rigid – left to right, respectively. The metal contact tip of the flexible probe is about 7 mm long.
Fig. 4. The console regulates cryogen flow, which is controlled by use of a foot pedal.

N_2O is the commonest cooling agent used in tracheobronchial cryotherapy. It is stored at room temperature in high-pressure bottles where the gas is in the liquid state. N_2O vaporizes at the metal tip of the cryoprobe, where it expands from a high pressure to atmospheric pressure (Joule-Thomson effect). This expansion lowers the temperature of the fluid and produces droplets of liquid and reaches an equilibrium of –89 °C at atmospheric pressure. These droplets strike the metal tip of the probe and remove heat from the wall of the probe as they evaporate. The heat exchanges only occur in the distal 1 or 2 cm from the expansion nozzle between high-pressure fluid coming in and low pressure gas exhausting. Thus, the cooling power occurs just where it is needed, and in a very short time, as the metallic mass to be cooled is very small. N_2O produces an almost instant cooling effect, is readily available and is a little more expensive than LN_2. Carbon dioxide (CO_2) is attractive as it achieves a low temperature (–79 °C), but when it expands at atmospheric pressure it produces snow. Nevertheless, it cannot be used in fine bore bronchial cryoprobes as the solid particles block the flow.

Cryotherapy Equipment

There are three parts in the cryomachine: the console (fig. 2, 3), the cryoprobe (fig. 4) and the transfer line that connects the console and gas cylinder to the probe. The cryoprobes are rigid, semirigid or flexible (fig. 4). Rigid

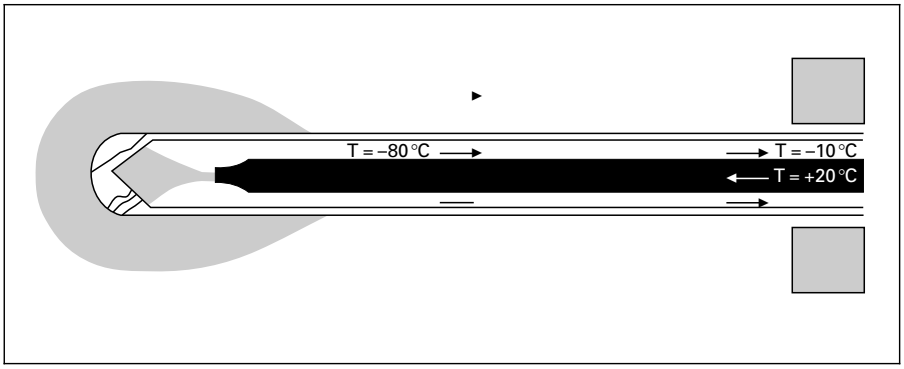


Fig. 5. The cryogen flows through the central channel of the probe, cooling the tip as it exits and vaporizes, then the vapors exit through the outer channel.

and semirigid cryoprobes can only be used through a rigid bronchoscope, whereas flexible cryoprobes can be used through the channel of the fiberoptic bronchoscope as well as with the rigid bronchoscope. The diameter of the flexible probes [29, 38–40] requires the use of the largest working channel fiberoptic bronchoscope available (2.6 or 3.2 mm).

The monitoring of the freezing remains a problem [54] and there is no ideal solution. The empirical method relies on the experience of the operator, and the operator relies on the change in color/consistency of the frozen tissue, and the length of freezing. In clinical studies [60, 61], using rigid, semirigid or flexible probes, each freeze-thaw cycle lasts about 30 s. The thaw phase is almost immediate with rigid probes that have a system of reheating; but with the flexible probes thawing takes place with body warmth, thus increasing the freeze/thaw cycle times.

The only method of monitoring freezing using an endoscope is the bioelectric method (fig. 2) [62]. The fact that complete extracellular crystallization is essential to produce tissue necrosis, this change in the physical state of the extracellular milieu during freezing (crystallization) leads to a change in the impedance of the tissue. When cryotherapy is used, the cryoprobe represents one electrode, and the other is a metal plate placed in contact of the patient's body. The ice ball that is formed breaks the current between the two electrodes, and when a resistance of between 200 and 500 kW is reached, this shows that the cryoprobe is working correctly.

Endoscope Equipment

The selection of the cryoprobe will depend on whether rigid or flexible bronchoscopy is used. The use of rigid bronchoscopy seems to be the preference in Europe (fig. 2). The flexible and a semirigid probe are used with the flexible bronchoscope (fig. 4). N_2O cools the probe tip to about –89 °C (fig. 5). The temperature increases about 10 °C per mm from the tip (a warming effect); so the effective 'killing zone' is about 5–8 mm. A flexible bronchoscope with a working channel diameter greater than the probe (flexible probe diameter is 2.2 mm, semirigid is 2.6 mm) is needed. Furthermore, the probe may expand slightly with cooling. The probe is attached to a console which regulates the coolant flow (fig. 3).

The minimum diameter for a rigid adult bronchoscope is 8 mm for endobronchial cryosurgery to be carried out under direct vision. Rigid probes have certain advantages: (1) there is a larger area of destruction due to its larger diameter; (2) they have a reheating system by interrupting the return of the decompressed gas. This reheating shortens the freeze/thaw time and allows the probe to be moved to another area. The duration of the freeze/thaw cycle is about 25 s with rigid probes to 2 min with flexible probes. In general, rigid probes are less fragile than flexible ones. Yet, flexible probes are still important for treating small lesions, accessing the upper lobes, and extracting foreign bodies.

Indication and Patient Selection

The key factor for successful tracheobronchial cryotherapy is not only the technique but more so the indications. Choosing endobronchial cryotherapy is based on several factors. The patient's symptoms and signs should be attributable to an endobronchial obstruction. A histological diagnosis should be obtained; if curative treatment is not an option then palliation is the objective. In any case, the patient must be able and willing to undergo bronchoscopy.

If the patient has impending respiratory failure due to an obstructing tumor or a stenosis, then surgery, laser, electrocautery, stent placement or combinations of these modalities are options, since cryotherapy is often ineffective in removing tissue rapidly (see chapter by Bolliger on Multimodality Treatment of Advanced Pulmonary Malignancies, pp. 187–196).

Additionally, the lesion must be accessible to the cryoprobe through the bronchoscope. Lesions that are polypoid, of short length, have a large endobronchial component, allow some visibility beyond the lesion and have functioning lung distal to the lesion are prime candidates. Long tapering lesions or those with extensive submucosa involvement are unfavorable. Similarly, if extrinsic airway compression is the cause of the problem, then an alternative treatment must be considered.

The role of cryotherapy in carcinoma in situ, dysplasia or other premalignant states of bronchogenic carcinoma is under investigation. A European multicenter study is currently in progress [63]. Apart from malignancies, cryotherapy can be used to remove foreign bodies, mucus plugs or blood clots, to treat granulation tissue or stenoses alone or with other adjunctive therapy (balloon dilation, stent placement) and to treat benign airway tumors.

Preparation of the Patient

An initial endoscopy is done along other routine examinations such as chest X-ray, CT scan, coagulation studies, blood gases and respiratory function.

Rigid Bronchoscopy

Rigid bronchoscopy can be carried out under neuroleptic analgesia or general anesthesia. An intravenous infusion is started followed by local anesthesia of the pharynx. Usual monitoring includes an electrocardiogram, blood pressure recording, and arterial oxygen saturation. For procedures performed under general anesthesia, a period of preoxygenation is followed by induction of anesthesia with propofol, and complete relaxation is provided with fentanyl. The procedure lasts between 20 and 30 min. Rigid bronchoscopy allows satisfactory oxygenation and ventilation. In our institution, the anesthetists prefer manual ventilation, rather than jet ventilation.

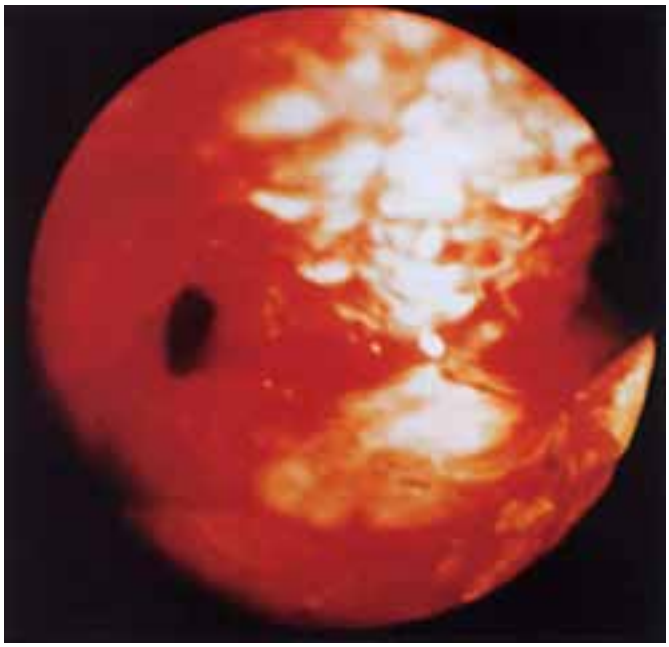


Fig. 6. Infiltrative aspect of the main carina due to an adenoid cystic carcinoma: excellent indication for cryotherapy.

Technique

Rigid Bronchoscopy

The patient is placed in the supine position, and the endoscope is introduced. The lesion is inspected to see the location, degree of stenosis, extrinsic compression, infiltration (fig. 6) and whether there is hemorrhagic tendency. If there is a risk of bleeding, carrying out an initial freeze/thaw cycle will be done. In this manner, the hemostatic properties of cold are used. The freeze/thaw procedures are carried out under direct vision via the telescope. The distal tip of the rigid bronchoscope should be placed about 0.5–1 cm above the lesion.

The metallic tip of the cryoprobe is placed on the tumor or pushed into it, which produces circumferential freezing of maximal volume (fig. 7). Three freeze/thaw cycles are carried out at each site. The probe is then moved 5–6 mm and another 3 cycles carried out in the adjoining area [64, 65]. The points of impact are staggered, with an overlap of the frozen zone with respect to the previous site. The procedure is continued until the entire visible part of the tumor has been frozen. The most suitable types of lesions are polypoid ones, benign or malignant. With infiltrating lesions, cryotherapy can be used with lateral tangential contact (fig. 8).

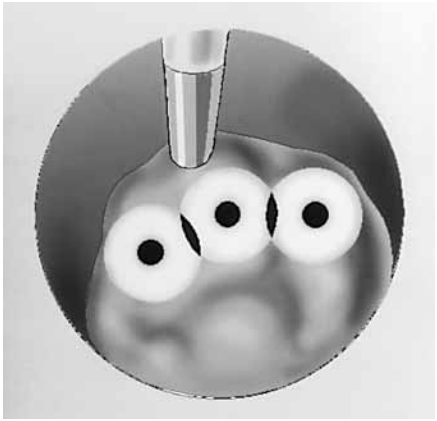


Fig. 7. Tissue can be frozen applying the probe perpendicular to the tissue. Overlapping the freezing fields will maximize tissue destruction.

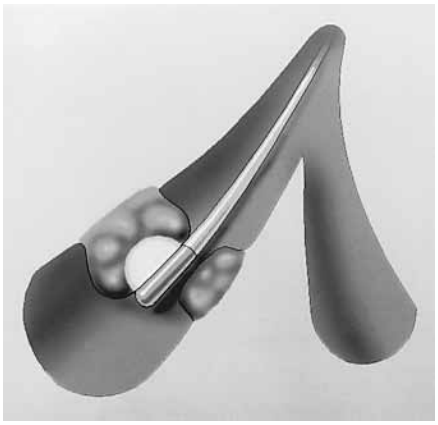


Fig. 8. Cryotherapy can be accomplished by applying the probe to the lesion tangentially.

If the probe is equipped with a device for measuring the impedance, reheating is achieved when a plateau is reached (between 250 and 500 kΩ according to the tissue and position of the cryoprobe). Subsequent cycles are commenced when the impedance has fallen to 50 kΩ but before the probe has become unstuck. With the other N_2O-driven cryoprobes, the freezing time is around 30 s per cycle. There is no value in prolonging the freezing beyond this time, and it has been shown that there is a greater cryodestructive effect when several freeze/thaw cycles are used.

Eight to 10 days after the first session, a repeat bronchoscopy is usually done, most often with a flexible bronchoscope. This examination enables assessment of cryodestruction, removal of any slough, and repeats cryotherapy if required. This is generally the case with voluminous tumors. The slough may be removed by forceps, aspiration or with the cryoprobe by using cryoadhesion.

Fiberoptic Bronchoscopy

The patients undergo routine fiberoptic bronchoscopy with standard monitoring in a fully equipped bronchoscopy suite. Before the bronchoscopy, routine clinical data are obtained: Arterial blood gases, coagulation parameters, and chest X-ray. An intravenous access site is established and normal saline infusion is used during the procedure. Monitoring includes an electrocardiogram, blood pressure recording and arterial oxygen saturation. Supplemental oxygen is given and the bronchoscopy is done in a standard fashion with premedication of atropine. Topical anesthesia of the oro- and nasopharynx is achieved with 5% lidocaine. Conscious sedation is achieved with intravenous midazolam and meperidine or morphine.

The fiberoptic bronchoscope is passed through the nose or orally in the usual fashion; however, oral intubation through an endotracheal tube allows easy removal of any tissue, debris or foreign bodies and allows for airway control should bleeding occur. A thorough inspection of the tracheobronchial tree is completed. (similar to the rigid bronchoscopy). Endoscopic therapy is then performed using a flexible cryoprobe (ERBE USA Inc., Marietta, Ga., USA) [28, 38–40] which is passed through the working channel. The cryoprobe tip is visualized and applied to the tumor area. N_2O cools the probe tip to about –89°C. The cryoprobe is activated with a foot pedal. The cryoprobe should be kept about 2 mm away from the tip of the bronchoscope. An ice ball appears within 30 s on the tip of the probe; three freeze/thaw cycles each lasting for 1 min are applied to the same area. Similar to rigid bronchoscopy, the tip is moved to an adjacent area until the whole lesion is completely frozen (fig. 7). The tip of the probe could be applied perpendicularly, tangentially or driven into the tumor mass (fig. 8). The tissue is frozen at –30 to –40°C. The cryodestruction becomes visible. With release of the foot pedal, the iceball thaws. Now the probe can be retracted or removed. When attempting to remove material from the airway, retraction of the probe after release of the foot pedal (but before iceball thawing) maintains probe-material adherence. Occasionally, suctioning of blood or secretions between applications is necessary. Any devitalized or necrotic tissue can be removed with a biopsy forceps during or before

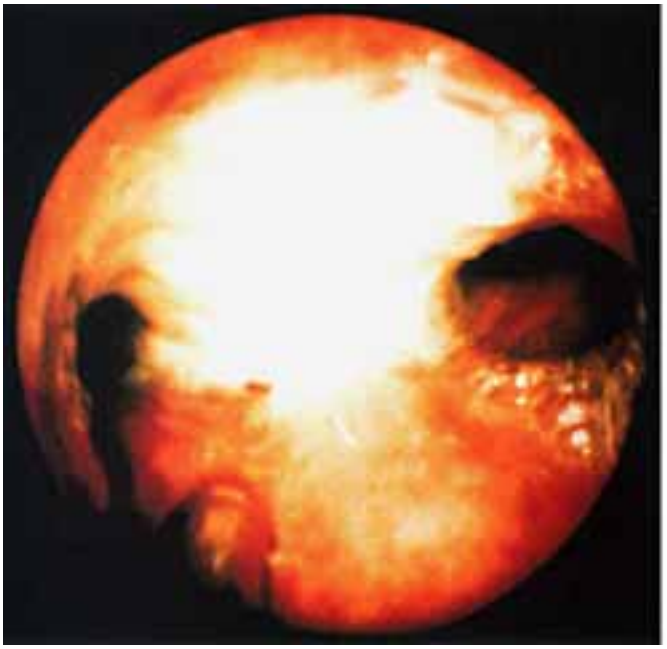


Fig. 9. Necrotic slough 2 weeks later, just before the mechanical extraction.

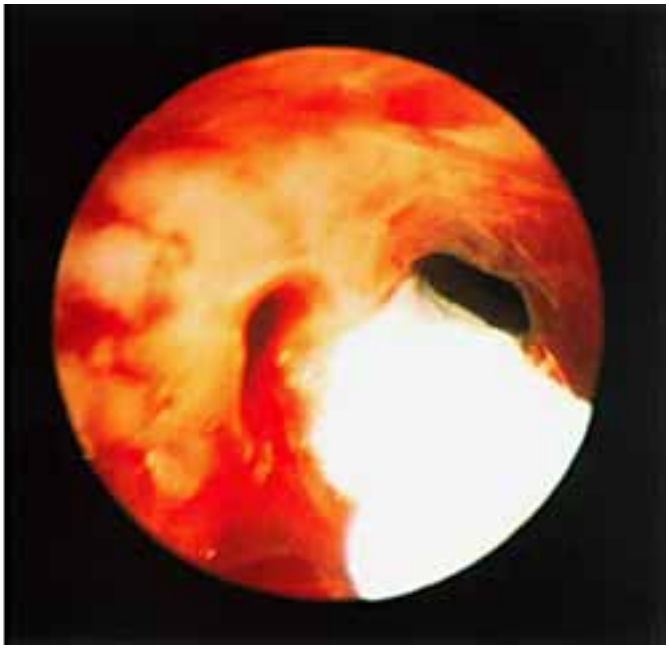


Fig. 10. Treatment with cryotherapy of an 'in situ' cancer located on a spur in a right lower lobe.

completion. Bronchoscopic examination is repeated 1–2 weeks later, when either more cryotherapy can be applied, and/or the slough is removed (fig. 9). Additionally, any adjunctive treatment can be done at the same session as cryotherapy.

Postoperative Care

Cryotherapy does not require any particular immediate follow-up care. After a general anesthetic keeping the patient under medical surveillance for 24 h is prudent. However, when local anesthesia and conscious sedation are chosen, the patients are sent home on the same day. A chest X-ray immediately after therapy is not essential, but is usually done. Occasionally, rapid relief of bronchial obstruction may be achieved by retraction of tumor tissue after freezing, and reventilation of an area (lobe or lung) may be confirmed. Nevertheless due to the delayed effect of cryonecrosis, there is generally no immediate change in a chest X-ray.

Administration of corticosteroids is not routine and is only suggested following treatment of laryngeal or tracheal lesions, where there is a risk of edematous reaction. The hemostatic effect of freezing is often sufficient to stop hemoptysis, but it may be delayed and only occur some hours or the day after cryotherapy. Moreover, the trauma caused by the penetrating probe into an already hemorrhagic lesion may temporarily aggravate the bleeding.

Clinical Basis for Cryotherapy

The results of cryotherapy are judged by several different means: endoscopic appearance, clinical criteria, radiological changes, changes in respiratory function, and histological appearance, Walsh et al. [33] reported the effects of cryotherapy on dyspnea, cough and stridor. In their study, symptoms, lung function, chest radiography and bronchoscopic findings were recorded serially before and after 81 cryotherapy sessions in 33 consecutive patients. In most patients the overall symptoms, stridor and hemoptysis improved, and they had an overall improvement in dyspnea. Similarly, Maiwand and Homasson [36] reported on 600 patients treated with cryotherapy at Harefield Hospital in London. Following cryotherapy, 78% of the patients noticed a subjective improvement in their condition. These patients had less cough (64%), dyspnea (66%), hemoptysis (65%) and stridor (70%) [32]. Homasson et al. [26] described that hemoptysis stopped

Table 2. Indications for cryotherapy and endoscopic therapeutic modalities in the treatment of lung cancer

	Cryo-therapy	YAG laser	HF electro-coagulation	Photo-dynamic therapy	Stents (silicone)	HDR brachy-therapy
Tracheal tumor with acute dyspnea	no	++++	++++	no	no	no
Tracheal or mainstem tumor with acute dyspnea	+++	++++	++++	+	no	+++
Peripheral tumor	+++	+	+++	++	no	+++
Well-limited infiltrative tumor	++++	no	+++	+++	no	+++
Infiltrative tumor within precise limits	+++	no	++	++++	no	++++
'In situ' or microinvasive tumor	+++	+	ND	+++	no	+++
Coagulation	++++ delayed	+++ immediate	+++ immediate	ND	possible	++++ delayed
Extrinsic compressions, dyskinesia	no	no	no	no	++++	++

ND = Not done.

Table 3. Comparative results of cryotherapy and other endoscopic therapeutic modalities

	Cryotherapy	YAG laser	HF electro-coagulation	Photo-dynamic therapy	Stents (silicone)	HDR brachy-therapy
Hemoptysis control, %	65–86	60	90	ND	possible	80
Cough/dyspnea improvement, %	66	80–90	50–60	70	90	85
Functional test improvement, %	50	85	73	ND	71	80
Airway clearance, %	75 delayed	90 immediate	84 immediate	50–60 delayed	90 immediate	80 delayed
Benefit duration, months	3–4	2–3	ND	ND	4	6.5
Ability to repeat treatment	yes	yes	yes	yes	yes	no
Curative effects (early cancers)	yes (89%)	in rare cases	yes (84%)	yes (77–85%)	no	yes (84%)

ND = Not done.

in 80%, and dyspnea decreased in 50% of cases [26]. Other symptoms that showed changes were those of wheeze, cough and thoracic pain. Similar findings were reported in a smaller number of patients when cryotherapy was performed using a fiberoptic bronchoscope [28, 38]. Objective improvement of pulmonary function was seen in 58% of patients, and these changes in lung function correlated with symptoms shown by Walsh et al. [33].

For malignant tumors, cryotherapy will destroy only the visible endobronchial portion, and therefore, the results are difficult to assess, as they depend on various criteria, namely, endoscopic appearance and tumor histology. Cryotherapy is a palliative treatment in these cases, and overall, the results are favorable in between 70 and 80% of patients treated, according to the criteria used to measure performance. It invariably improves the quality of life by reducing some unpleasant symptoms of bronchial obstruction, but there has been no significant improvement in survival.

There has been a renewed interest in treatment of early stages of lung cancers (fig. 10). The French experience [63] reported by the GECC (study group on cryosurgery) is based on 36 patients with 44 lesions (in situ or microinvasive tumors). Forty-two percent of these patients had been treated for an invasive ENT or bronchial cancer. At 1 year, complete clinical and histological control of the

tumor was achieved in 89% with a mean follow-up of 32 months. The mean survival of this population was 30 months. Failures of cryotherapy were in lesions with poor demarcation or distal, poorly accessible locations. Other techniques have shown similar results in early-stage lung cancer, but cryotherapy may offer the best efficency/tolerance ratio (tables 2, 3).

Cryotherapy for Benign Tracheobronchial Lesions

Benign tracheobronchial lesions constitute a small percentage of pathology seen in the tracheobronchial tree. Benign lesions have been treated with cryotherapy with very good results, particularly for granulomatous tissues; 100% had favorable results with no recurrence months or even years after treatment [38]. Granulation tissue is very sensitive to the effects of cold. Cryotherapy has also been successful in treating tumor or granulation tissue regrowth around both silicone or wire mesh stents without the loss of the integrity of the stent.

Tumors of low or intermediate malignancy are rare and very few have been treated with cryosurgery. Nevertheless, when surgery is not possible, treatment with cryotherapy can yield good results, and several cases of carcinoid, cylindromas (fig. 6), mucoid squamous cells, and laryngotracheal papillomas have been successfully treated. Good results have been obtained when treating myomas and leiomyomas, although several sessions may be needed. Less vascularized lesions, such as amyloidosis, fibromas, lipomas, hamartochondromas or fibrous stenoses, are rarely influenced by cryotherapy. Although technical complications after lung transplantation have become rarer, stenoses at the anastomotic site still occur with granulation tissue being the commonest presentation. Usually a web-like stenosis is found which is perfectly amenable to cryotherapy. Twenty-two patients with tracheal or bronchial stenosis, unresponsive to dilation when treated, had a patent lumen restored after cryotherapy [38].

Removal of Foreign Bodies

Foreign bodies have been extracted successfully using cryotherapy. They include pills, peanuts (fig. 11), teeth, chicken bones as well as blood clots, mucus plugs and slough [38, 40].

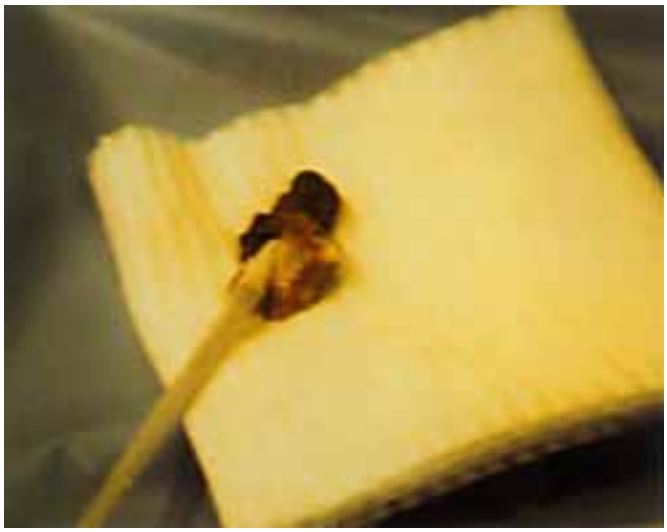


Fig. 11. Removal of a nut blocking the bronchus intermedius with cryoadhesion.

Associations of Cryotherapy with Chemotherapy or Radiotherapy

Cryotherapy – Chemotherapy

It has been shown [54] that chemotherapy is more effective following cryotherapy in oral cancer. Drugs seem to accumulate at the tumor site immediately following cryotherapy. Using an experimental murine tumor preparation, Ikekawa et al. [55] investigated the efficacy of cryotherapy and confirmed the phenomenon of drug trapping after combined treatment. A prospective study performed at Chevilly-Larue, France, confirmed these experimental data in 12 patients [43]. All patients were inoperable with endobronchial tumor obstructing one main bronchus. All received intravenously 15 mg of bleomycin labeled with cobalt-57. The endoscopic treatment was carried out using either a rigid or a flexible cryoprobe. A significant difference was found in the tumor uptake of radio-labeled bleomycin before and after cryotherapy with a mean increase of 30% in the tumor-to-normal tissue ratio. It can be postulated that bleomycin is trapped in the tumor because of the vascular disruption caused by freezing. This study thus confirms the experimental findings of Ikekawa et al. [55] and offers an explanation for the findings reported by Benson [54]. Although this series is too small to draw any meaningful conclusions, combined cryo-chemotherapy is an intriguing concept.

Cryotherapy – Radiotherapy

In localized inoperable bronchial carcinomas, radiotherapy is an accepted treatment, but the mean survival of patients is only 20 months, and local eradication of tumors is obtained in only 35% of cases. In obstructive tumors, the reinflation of the lung is achieved after irradiation in only 21% of cases [42]. When these obstructive tumors have been removed with an Nd:YAG laser prior to irradiation, these has been a better survival and quality of life [66, 67]. Cryotherapy will also remove endobronchial obstruction, and studies have suggested a possible synergy between cryotherapy and external irradiation due to increased blood flow after cryotherapy [36, 66]. Le Pivert [62] showed the appearance of marked neovascularization by angiography 15 days after cryotherapy. This hypervascularization may increase the radiosensitivity. In two similar prospective studies, Vergnon et al. [42] and Homasson et al. [26] have studied the association of cryotherapy and radiotherapy. A satisfactory outcome was defined as >50% tumor destruction. Radiotherapy was started 2 weeks after cryotherapy. Our study group consisted of 29 patients. All patients had symptomatic unresectable endobronchial obstruction. One or two sessions of cryotherapy were done; cryotherapy was considered satisfactory in 16 cases and unsatisfactory in 13 cases with persistent tumor lesions. Twenty-one patients received 65 Gy, and 8 patients in poor general condition received 45 Gy.

The results were evaluated with flexible bronchoscopy and biopsy 2 months after the end of irradiation. In the unsatisfactory cryotherapy group (tumor removal <50%), the median survival was 5 months. In the satisfactory cryotherapy group (tumor removal >50%), the median survival was 11 months. This study does not prove the potentiating effect of cryotherapy on the effect of radiotherapy. However, it confirms several significant points: cryotherapy is a safe method and is successful in 70–80% of cases [42]. This study reinforces the interest already generated in eliminating an obstruction before irradiation to improve survival. The survival curves obtained correspond closely to those obtained using laser resection of endobronchial lesions. This study also confirms the inadequacy of radiotherapy alone in relieving a bronchial obstruction. This 'curative' local effect raises the possibility of increased tumor radiosensitivity, induced by the vascular effect of the cryotherapy.

Conclusion

Cryotherapy for endobronchial lesions has been shown to be an effective and safe therapy in a number of pathologies. In particular, the technique is extremely useful in patients with carcinoma of the lung and airway obstruction. A large majority of patients show improvement in symptoms and respiratory function. These benefits are achieved by using a technique which is safe, easy to perform, inexpensive and has few complications.

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Endoluminal Brachytherapy in Central Lung Cancer

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Summary

Brachytherapy means the direct placement of a highly radioactive source inside a tumor mass. This can be done either by implanting the source directly into the tumor, via the natural route (endoluminal brachytherapy) or by placing the source into the tumor bed during tumor resection. Endoluminal brachytherapy employing the afterloading technique with iridium-192 high dose rate (HDR) is largely applied for the curative and palliative treatment of endobronchial tumors due to its tumor-specific and long-lasting effect. Endoluminal brachytherapy using flexible bronchoscopy and an HDR regimen can be performed on an outpatient basis and is not more strenuous for the patient than a diagnostic bronchoscopy. Symptomatic improvement can be achieved in 70–80% of patients, and sometimes small tumors can even be cured. The afterloading procedure can be combined with all other modalities of tumor therapy. It can be used as 'boost' to conventional external irradiation and as local treatment modality in patients on systemic chemotherapy or as the only local treatment. HDR treatment is usually delivered with 1–6 fractions at an interval of 1–3 weeks and a dose of 3–20 Gy per fraction (at 1 cm from the source axis). In patients previously treated with external beam radiation therapy and in the palliative setting, a regimen of 7–10 Gy (HDR) per fraction and a total of 2–3 fractions per treatment is recommended. However, the optimal dosage and fractionation schemes for the tumor therapy are still unknown and there is need for further studies. In about 10% of the patients, radiation bronchitis occurs, and there may be fatal hemorrhage, possibly related to the therapy. Overall, endobronchial brachytherapy is a well-tolerated, not very aggressive treatment option, especially in patients with reduced performance status.

The majority of patients presenting with lung cancer have locally advanced or metastatic disease not amenable to curative surgical resection. Attempted resection with questionable or involved margins carries a high risk of subsequent local recurrence. Endobronchial metastases or local recurrence after surgery and/or radiotherapy often cause symptoms like dyspnea or hemoptysis due to tumor stenosis in the central tracheobronchial system. Apart from dyspnea, cough and hemoptysis, infectious complications are frequently encountered. Increased survival and improved local control can be achieved by combined chemotherapy and external beam irradiation (EBRT) for locally advanced inoperable lung cancer. However, there remains considerable need for improvement and for further local treatment options. Treatment should be quick, suitable for the patient and personnel, effective and carry a low risk for complications, because the treatment goal is mostly limited to palliation. For these patients, therapeutic tools suitable for the symptomatic management of these symptoms are available nowadays. The different local therapeutic modalities have special advantages and disadvantages. The best treatment option has to be chosen according to the individual situation, preferably using an interdisciplinary approach.

Amongst the currently available interventional bronchoscopic procedures, endobronchial brachytherapy is one of the oldest techniques. As early as 1922, the first successful endobronchial implantation of radium capsules (derived from gynecological implants) was documented, and many reports have followed since [1]. In the 1960s, cobalt-60 seeds were most frequently used as radiation source. Through brachytherapy, it is possible to deliver a maximum dose to the tumor with a minimum dose in the surrounding normal tissue. One of the major drawbacks of this method was the high level of radiation to which the medical personnel was exposed.

Therefore, the development of the afterloading technique was essential for the widespread application of brachytherapy [2]. The introduction of the iridium-192 radioisotope, and the refinement of the afterloading apparatus by using automated, computer-controlled steering devices, has meant significant progress [3]. The small size of the iridium source with its high activity and high dose rate (HDR) allows its placement in a hollow guidance catheter, which can be easily placed endobronchially by a flexible bronchoscope. Nevertheless, it was not until the widespread use of the Nd:YAG laser recanalization of tumor stenoses that endoluminal brachytherapy employing the afterloading technique with iridium-192 HDR was largely applied for the palliative treatment of endobronchial and parabronchial tumors.

Performed by an experienced endoscopist, HDR brachytherapy has as few acute side effects as routine fiberoptic bronchoscopy and can therefore be easily applied in an outpatient setting. Irradiation lasts some minutes only.

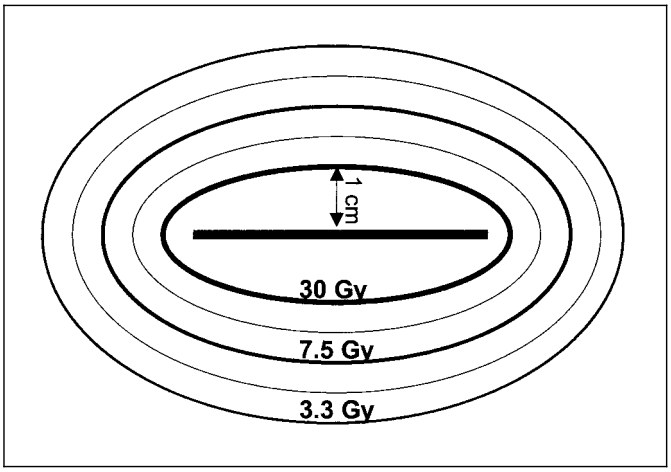


Fig. 1. Typical isodoses in HDR brachytherapy.

Technique

Brachytherapy (brachys = greek expression for 'short') means the direct placement of a highly radioactive source inside a tumor mass. This can be done either by implanting the source directly into the tumor (interstitial brachytherapy), via the natural route (endoluminal brachytherapy) or by placing the source into the tumor bed during tumor resection (intraoperative brachytherapy). The technical procedures to perform interstitial permanent volume or planar implantation of radioactive sources or interstitial temporary implantation are described elsewhere [4, 5]. Here we want to focus on the procedures of endoluminal brachytherapy which are commonly used.

As compared to conventional external radiotherapy, brachytherapy offers the potential advantage of providing a higher dose of radiation to the desired tumor volume by sparing normal tissues. The physical characteristics of radioactive isotopes are characterized by the inverse square law which means that the dose rate decreases as a function of the inverse square of the distance to the source centre. This makes it possible to achieve a high irradiation dose in the centre of the irradiation source with a fast decrease towards the periphery. A typical distribution of isodoses is shown in figure 1. For example, an irradiation dose of 30 Gy delivered at 1 cm from the source axis results in a dose of only 7.5 Gy at 2 cm and as little as 3.3 Gy at a distance of 3 cm. By employing the remote afterloading technique, the spinal cord receives not more than 5–10% of the dose prescribed at 1 cm in normal endobronchial brachytherapy [6]. On the other hand, when an inhomogenous tumor mass is not well localized, normal tissue adjacent to it is likely to receive very high irradiation doses. In order to spare normal tissue, it is necessary to place the irradiation probe carefully in the center of the tumor bulk and, whenever possible, to use devices which guarantee a constant distance.

Endobronchial or interstitial brachytherapy can be categorized as permanent or temporary. Permanent implants are characterized by a very low-dose irradiation rate (e.g. iodine-125). This type of radioactive source is infrequently used, most in tumor locations with no existing lumen, e.g. in a perioperative setting or pancoast tumors [4].

Temporary brachytherapy is most frequently used. This form of brachytherapy can be divided into three dose rate regimens: low dose rate (LDR, less than 2 Gy/h),

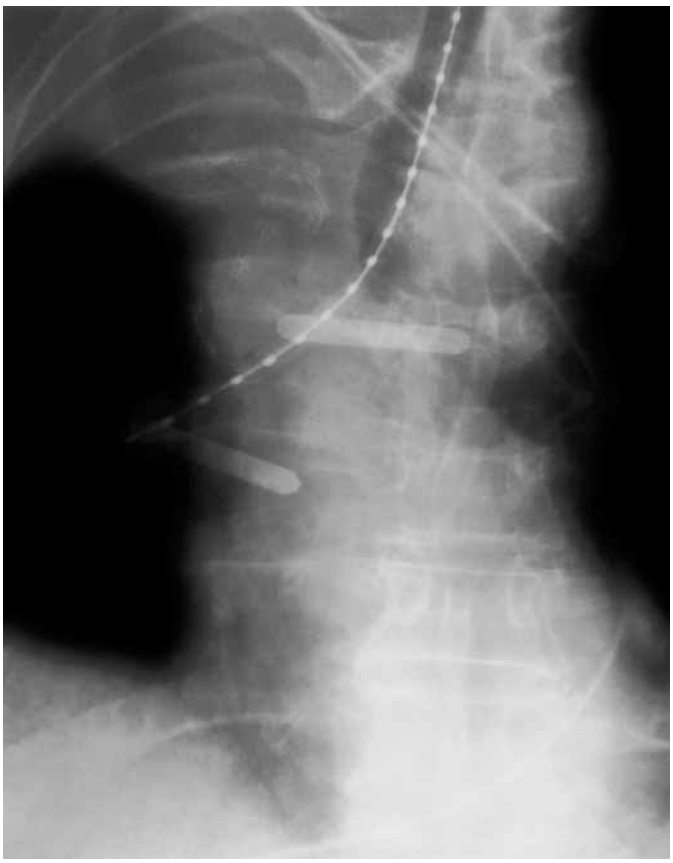


Fig. 2. Chest X-ray after placement of brachytherapy catheter in the right upper lobe with dummy seeds.

intermediate dose rate (IDR, 1–12 Gy/h) and HDR (more than 2 Gy/min). LDR brachytherapy usually requires 8–48 h of treatment time, while HDR is achieved within a few minutes. The common radioactive source is iridium-192 but cesium-137 or iodine-125 are also used.

Endobronchial treatment is achieved by placing one or two afterloading applicators within the trachea and the central bronchial system. In specialized centers, positioning of the afterloading probe as far as the subsegmental bronchi is possible (fig. 2).

The afterloading catheters have an external diameter of 2–3 mm. Flexible bronchoscopy is performed to localize the tumor region for irradiation. If there is subtotal stenosis of the bronchi due to submucosal or exophytic tumor growth, it is sometimes necessary to perform balloon dilatation or use other recanalization methods for better applicator placement. If there was previous laser treatment, it is recommended to wait at least 3 days before brachytherapy treatment can be initiated, although the debate about this issue is still ongoing [7, 8].

Endoluminal irradiation should be delivered with a 'safety' margin of at least 1 cm at both ends of the visible endobronchial tumor length. The active length refers to the distance between the first and last dwelling point of the stepping iridium source in case of HDR brachytherapy. As the distal end of the tumor can not always been seen by the bronchoscopist, the distal endpoint of the irradiation length must often be estimated from previous chest X-rays or CT scans and controlled during bronchoscopy by fluoroscopy.

The irradiation length is marked by external tags, controlled by fluoroscopy. A guidewire is placed through the working channel of the bronchoscope which is then removed (fig. 3a–c). Manipulation of the guidewire and then of the applicator through a partially obstructed lumen requires skill, particularly within the upper lobe bronchi.

For a better fit of the afterloading probe, we usually insert a shortened gastric tube with an external diameter of 5 mm by the Seldinger technique over the guidewire (fig. 4a–c). The gastric tube should be placed inside the tumor bulk. The irradiation applicator is then placed into the tube and taped to the tip of the nose to prevent it from being dislocated. This should be done under permanent visual fluoroscopic control.

After placement of the afterloading probe, a dummy seed is inserted, and a set of orthogonal chest X-rays is obtained to confirm the correct placement of the catheter within the tumor bulk and to determine the necessary irradiation length, as indicated by the external tags (fig. 5a–c). Treatment dose is prescribed by the radiation oncologist, usually specified at a depth taken 1 cm from the middle of source axis [9].

One of the technical challenges is the obvious difference in luminal diameters of different segments of the tracheobronchial tree. It is uncommon to adjust for these differences, but Saito et al. [10] tried to answer this problem by setting distinct diameters at different segments of the tracheobronchial tree and adjusting the dose evaluation point to the lumen diameter at the lesion site.

Remote brachytherapy is performed in a shielded room with permanent oxygen delivery to the patient, who is monitored from outside by continuous assessment of oxygen saturation, pulse rate or ECG and direct visual control through a video camera. The treatment can be interrupted and restarted whenever necessary.

After removal of the dummy seed, the applicator is connected to the iridium-192 remote afterloading unit.

The irradiation source (diameter about 1 mm) is advanced to the intended position under computer control and then drawn backwards at intervals of 5 mm distance. It remains in each position for the time needed to apply the computed dose. By varying the source position and dwelling time, individual computer-assisted dose distribution can be generated (fig. 6).

In general, endoluminal brachytherapy using flexible bronchoscopy and an HDR regimen can be performed on an outpatient basis, as it is not more strenuous for the patient than a diagnostic bronchoscopy. In the case of LDR brachytherapy, hospitalization for several days is usually required. Due to the development of high activity sources, HDR brachytherapy has now largely replaced the LDR treatment at most medical centers. HDR treatment is usually delivered as 1–6 fractions at an interval of 1–3 weeks. Controlled comparative data are widely lacking. More recently, hyperfractionated HDR has been explored in a pilot study with similar morbidity compared to conventional HDR or LDR [6], but the final data have not been published yet.

Acute side effects of the placement procedure include more or less severe coughing and increased bronchial secretion. Temporary pleuritic pain or even pneumothoraces have been described when the guidewire or the applicator was placed too vigorously [5]. However, we never observed such serious side effects during more than 1,000 placements of afterloading probes.

Indications for Endoluminal Brachytherapy in Central Lung Tumors

Carcinoma in situ and Early-Stage Non-Small Cell Lung Cancer

Surgical resection is widely accepted as the treatment of choice in early-stage non-small cell lung cancer (NSCLC). But when occult carcinoma in situ or small invasive endobronchial lesions are discovered incidentally by bronchoscopy due to early irritative symptoms like cough or hemoptysis, HDR brachytherapy either alone or as a boost to EBRT offers an excellent treatment option with good results, low morbidity, low costs and little inconvenience for the patient. Especially in carcinoma in situ or limited invasive tumors without nodal involvement, HDR brachytherapy could represent the definite treatment.

Due to the development of other treatment modalities (e.g. photodynamic therapy), data published on intraluminal brachytherapy in early-stage NSCLC are limited. Studies comparing these two treatment modalities are missing. Due to the deeper penetration, brachytherapy could be superior to the photodynamic treatment.

Stage II–IIIb (T3–T4, N0–N3), Curative Treatment Intention

In patients with stage II–IIIa, surgery is the treatment of choice whenever possible. Several attempts have been reported to improve survival by adding interstitial brachytherapy, but the data are sparse and conflicting [4, for review]. When the option for interstitial brachytherapy is available, it should be considered to enhance local control if complete surgical resection is not possible. Unfortunately, up to one third of newly diagnosed patients with NSCLC present with locally advanced, unresectable disease [11].

External radiotherapy has a potential for cure in only few patients, and local recurrences are even more frequent [12, 13]. Nevertheless, this treatment modality can improve symptoms for those patients who are inoperable due to locally advanced disease or other medical reasons as well as in a palliative situation.

In spite of high doses of 50–60 Gy, median survival is approximately 1 year, and long-term survival rates are less than 10% [13].

To increase the cumulative dose of irradiation, additional endobronchial brachytherapy has become more widely used [14–21]. Brachytherapy has been applied as a boost either before, during or after EBRT. HDR brachytherapy has been primarily used for previously untreated patients in conjunction with EBRT, often to relieve obstruction quickly and to reduce the volume of irradiated normal lung tissue. Particularly, when atelectasis due to obstruction of a main or global bronchus is obscuring the true tumor margins, brachytherapy can help to reduce the permanent fibrosis of normal lung tissue due to large external irradiation fields. It has been calculated that this procedure can reduce the irradiation of normal tissues by an average of 32% [22].

Apart from treatment for local stenosis, brachytherapy has the potential to increase survival time and local control when used in combination with external irradiation. Although none of the studies published so far could demonstrate a clear advantage in terms of survival in nonselected patients treated with this combined modality, there are indications that at least local control is better in patients with additional endoluminal brachytherapy. Again, larger, multicenter, controlled, prospective and randomized studies are needed to evaluate this promising treatment regimen.

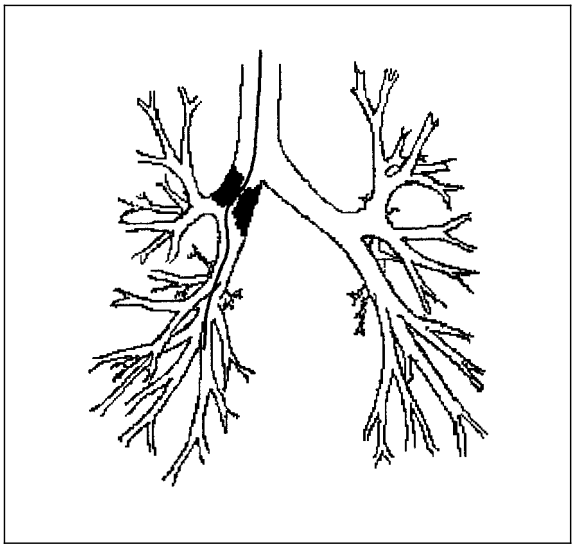
Although it is often difficult to differentiate between treatment complications and tumor progression, it is possible that the combination of external and endoluminal irradiation increases the frequency of hemorrhages, perhaps due to the proximity of the afterloading catheter to pulmonary vessels.

Stage IV, Tumor Recurrency, Palliative Treatment Intention

Endobronchial brachytherapy is a relatively simple, fast and minimally invasive method to relieve bronchial obstruction or to maintain airway patency. Therefore, HDR brachytherapy is now a frequently used treatment option in patients with relapsing endobronchial tumor, with thoracic metastases from other primaries, poor overall performance status, or for patients unwilling to undergo other (i.e. chemotherapeutic) intensive treatments.

Although the term 'palliative' is difficult to define, palliative HDR brachytherapy should be considered in every patient presenting with symptoms of endobronchial tumor growth (hemoptysis, cough, atelectasis, dyspnea, pain) if other definite treatment modalities (i.e. surgery, EBRT multimodal therapies) are not available for the patient for any reason.

Compared to photodynamic therapy, endobronchial stenting or balloon dilatation, endobronchial brachytherapy is probably more effective to maintain long-term airway patency and symptom relief. In most of the published studies on palliative brachytherapy, overall improvement of symptoms has been shown in 65–95% of all patients. Especially hemoptysis can be treated with a high rate of success, this is also true for the reopening of obstructed bronchi. Improvement of cough, shortness of breath and pain was observed to a lesser degree. Palliation can be maintained in a high proportion of patients [6, 16, 18, 23–34].



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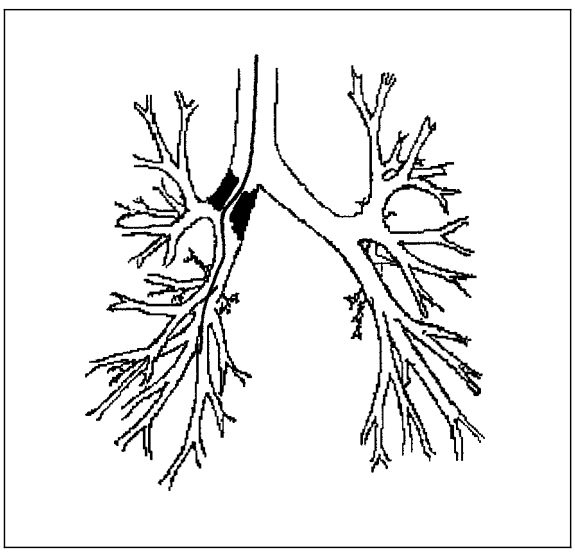

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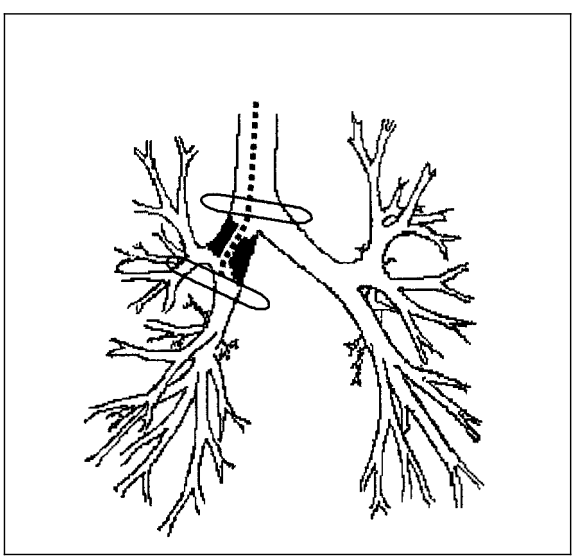

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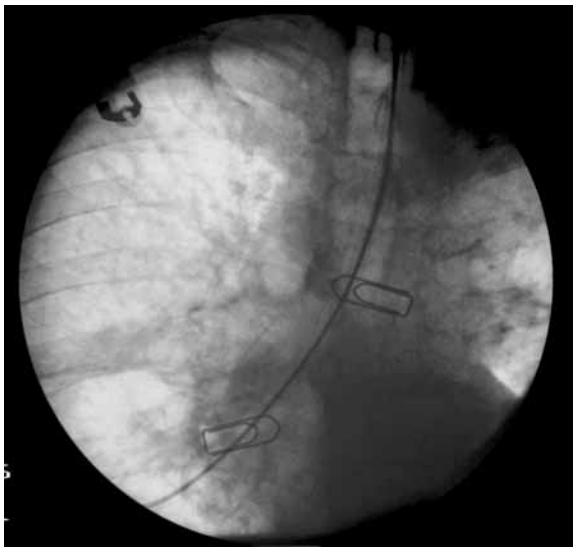
Fig. 3–5. Endobronchial afterloading technique. **3** Insertion of the guidewire. **a** Schematic illustration. **b** Fluoroscopy. **c** Endoscopic view. **4** Insertion of a shortened gastric tube over the guidewire (Seldinger technique), then removal of the guidewire. **a** Schematic illustration. **b** Fluoroscopy. **c** Endoscopic view. **5** The afterloading applicator with the dummy seed is inserted through the stomach tube, then the necessary irradiation length is determined by using external tags with fluoroscopy (here: 6 cm length), then the dummy seed is removed. **a** Schematic illustration. **b** Fluoroscopy. **c** Endoscopic view.



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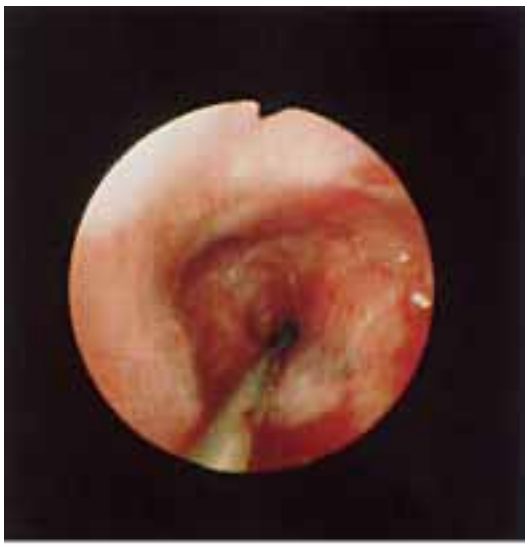

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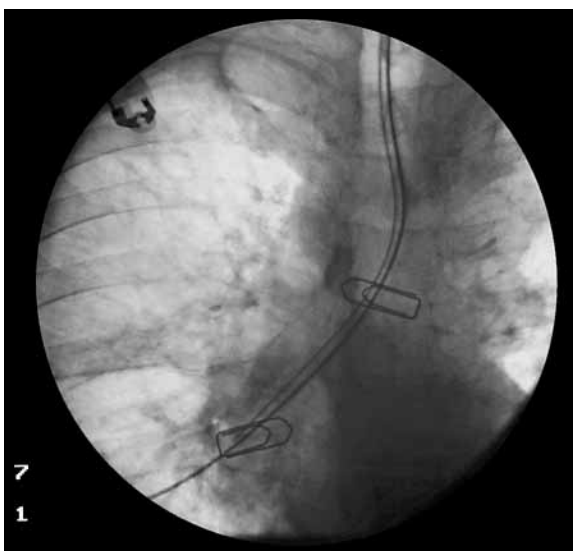

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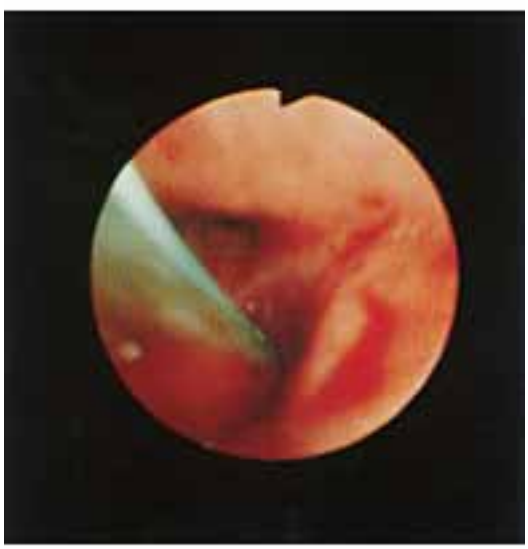

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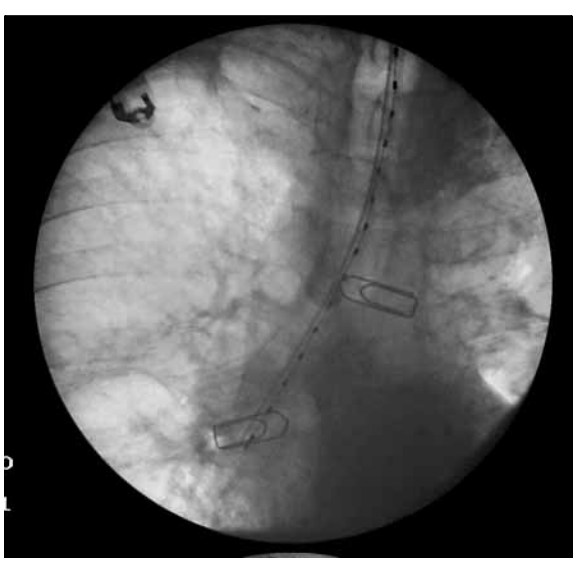

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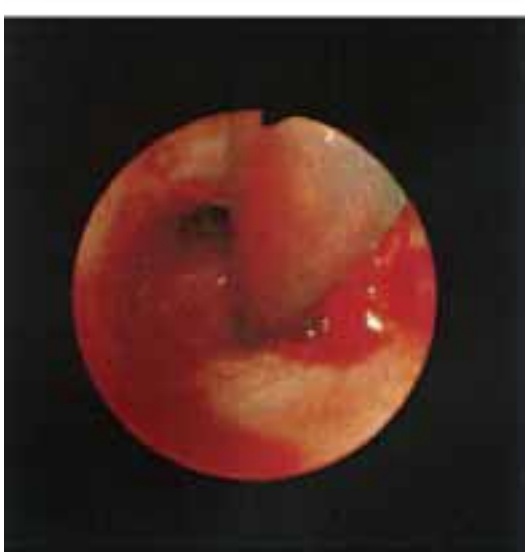

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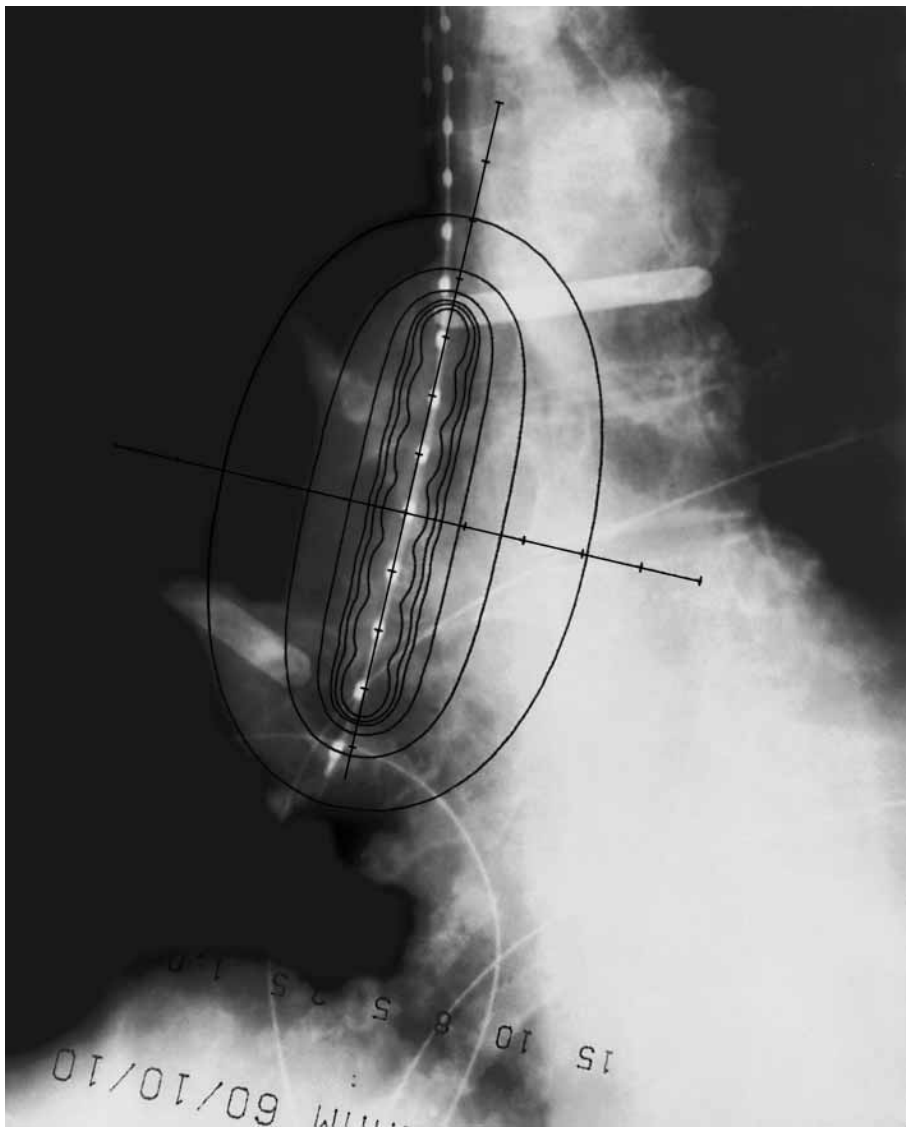


Fig. 6. Determination of the necessary irradiation length by external tags with fluoroscopy and distribution of the typical HDR brachytherapy isodoses.

Table 1. Results of some studies on HDR brachytherapy

Authors	Patients	Prior treatment (laser, stent, chemotherapy), %	Total EBRT Gy	Total HDR brachytherapy Gy range	Bronchoscopic response, %	Median survival weeks	Fatal hemorrhages %
Aygun et al. [14]	62	0	61	12–30	56	56	15
Cotter et al. [15]	48	0	66	6–35	86	32	5
Huber et al. [17]	42	18.6	50	7.4	74	27	18.9
Kohek et al. [20]	39	52	70	5.6–27.2	67	56	5
Speiser and Spratling [33]	50	24	60	22.5–30	80	44	7

Review of Published Results in Endobronchial Brachytherapy

Carcinoma in situ and Early-Stage NSCLC

There are no prospective, randomized studies evaluating the effect of endobronchial brachytherapy alone in the treatment of very early lung cancer, but some results are promising and merit further study.

Tredaniel et al. [35] treated 29 patients with stage I and II disease with endoluminal brachytherapy alone. They delivered a dose of 7 Gy (at 1 cm from the source axis) every second week, with a maximum of 6 fractions. After 2 months, histologic complete response was seen in 72% of the patients. After 23 months of follow-up, median survival has not yet been reached. Fatal hemoptysis occurred in 17% of the patients, although it was not clear if recurrent disease was the reason for this complication.

Sutedja et al. [36] treated 2 patients with LDR brachytherapy, demonstrating feasibility and showing good overall response.

Saito et al. [10] studied prospectively the effect a combination of EBRT with 40 Gy in 20 fractions and additional LDR brachytherapy (using a new technique with 4 thin iridium-192 wires) with 25 Gy in 5 fractions. Out of 39 evaluable patients, recurrent disease was observed in only 2 cases, which could be treated by subsequent surgery. The median follow-up period was 24.5 months. Other recurrences or severe complications from irradiation had not occurred. Second primary cancers were observed in 19 (lung 10; other organs 10) of a total of 41 patients [10].

Stage II–IIIb (T3–T4, N0–N3), Curative Treatment Intention

Endoluminal brachytherapy as sole treatment has not been published for this disease stage. Although LDR and IDR brachytherapy in combination with EBRT have been described, most experience exists with HDR brachytherapy as a boost to definite external radiation therapy. The results are summarized in table 1.

Higher combined doses of EBRT and brachytherapy have been associated with increased overall response, although this was not found by all published studies. Overall response rates, often assessed several months after completion of treatment, were good. However, the overall median survival time (7–13 months) is not higher than in patients treated with EBRT alone.

The only prospective, randomized study was performed by Huber et al. including a total of 98 patients. Two groups were compared: one group was treated with external radiotherapy alone (planned dose 60 Gy), the second group received an additional boost of HDR brachytherapy (4.8 Gy scheduled, at 10 mm from the source axis) before and after external irradiation. The mean total external irradiation dose was 50 Gy in both groups. The HDR brachytherapy group received an additional dose of 7.44 ± 2.6 Gy (at 10 mm depth). The median survival time in both groups was comparable (28 and 27 weeks, respectively). The low overall survival time in this study is probably due to the very low performance status of the patients (average Karnofsky performance status 65), compared to that of other, nonrandomized studies. In patients with squamous cell carcinoma (68 patients), the HDR brachytherapy group showed an advantage in median survival with borderline significance (40 vs. 33 weeks, p = 0.09). They also showed a better local tumor control (fig. 7). As could be expected, patients with squamous cell carcinoma had a significantly longer period of local tumor control. Fatal hemoptysis was the cause of death in 11 (18.9%) compared to 6 (14.2%) patients in the group treated conventionally.

Although, to our knowledge, further randomized studies to standardize the dose/fractionation regimen are not

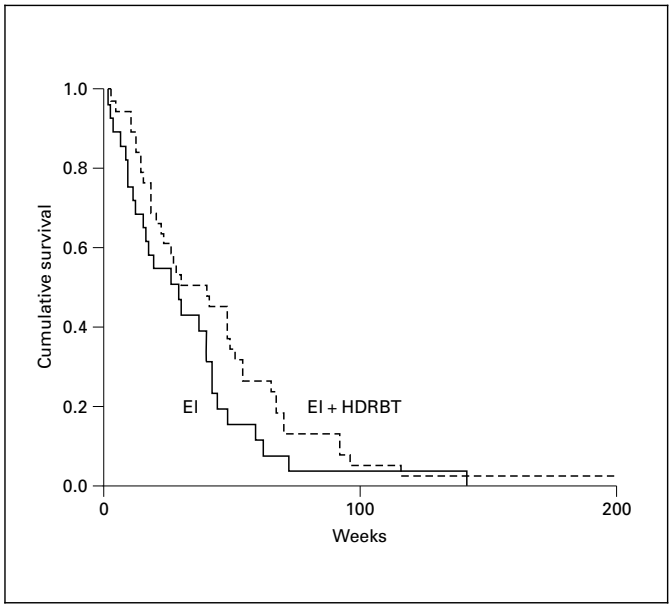


Fig. 7. Survival for patients with squamous cell carcinoma. EI = External irradiation alone (group 1; n = 29), EI + HDRBT = external irradiation and additional HDR brachytherapy (group 2; n = 39), censored (+) cases in group 1: 2; censored (+) cases in group 2: 1; Kaplan-Meier plot, p = 0.09 (log-rank test) [17].

Table 2. Comparison of some larger study series reporting experiences with different treatment regimens

Authors	Patients	Mean number of fractions/mean total dose, n/Gy	Overall response, %	Median survival time, weeks	Fatal hemorrhages, %
Bedwinek et al. [25]	38	3/18	41–82	26	32
Gauwitz et al. [40]	23	2/18	88	32	4
Gollins et al. [27]	406	1/15–20	46–92	26	8
Huber et al. [30]	93	2–4/15	41–49	19	21
Mehta et al. [6]	31	4/16	85	na	7
Speiser and Spratling [33]	342	3/22.5	85	22–26	7

na = Not available.

available, the following treatment regimen has been proposed: 60 Gy EBRT given over 6 weeks and a boost of 3 fractions of brachytherapy with 7.5 Gy each [5]. As this form of treatment has to be considered investigational, patients should be treated preferentially in controlled studies.

Stage IV, Tumor Recurrence, Palliative Treatment Intention

As mentioned above, one of the main indications for endobronchial brachytherapy is the palliation of symptoms due to uncontrolled bronchial tumor growth. Accordingly, many reports have been published reporting experiences with different treatment regimens [6, 7, 9, 16, 18, 25, 27, 30, 32–34, 37–40]. A comparison of some larger series is shown in table 2.

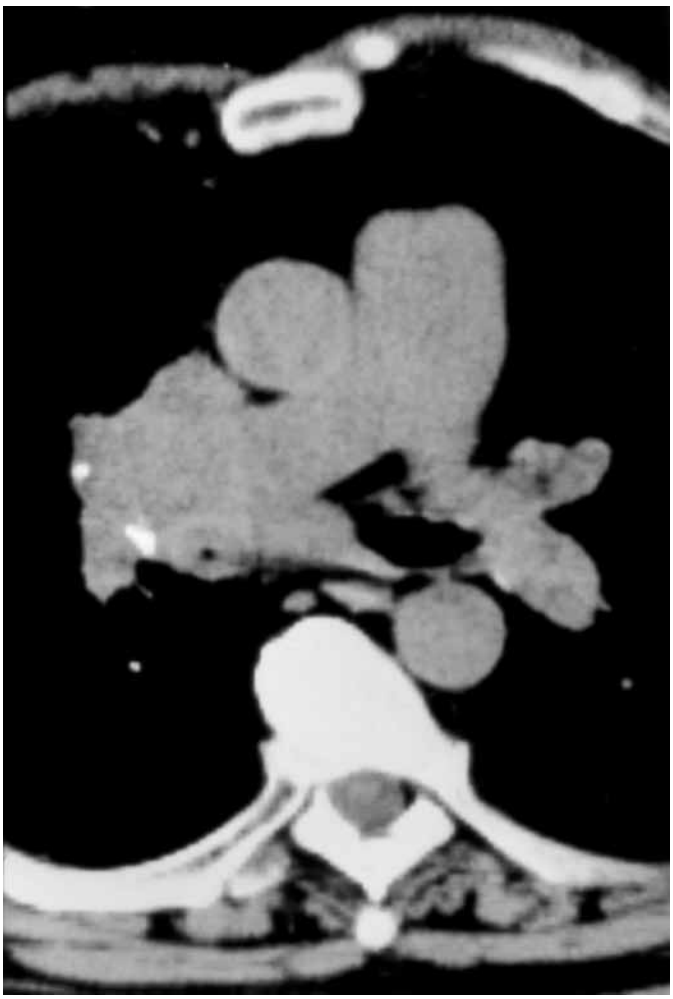
To our knowledge, there is only one controlled, randomized study to evaluate the effect of dose rate, overall radiation dose, fractionation and localization of the afterloading catheter to survival rate, local control and complications. In this study, Huber et al. [30] compared two treatment regimens with a comparable total irradiation dose of 15 Gy (at 1 cm from the source axis), but different doses per fraction (4 fractions of 3.8 Gy on a weekly basis, and 2 fractions of 7.2 Gy at a 3-week interval). They found no disadvantages for the shorter fractionation regimen with a similar survival time (19 weeks) and local control time in both groups. The complication rate was also similar with fatal hemorrhage occurring in about 21% of all patients.

In a nonrandomized study, Speiser and Spratling [33] treated a large series of patients to find the optimum dose and fractionation for patients with central lung tumors. Different treatment regimens were tested subsequently with three levels of brachytherapy doses. Regardless of the limitations of their methods, their conclusion is that the most effective dose fractionation is 7.5 Gy in 10 mm depth for 3 fractions once a week. There was no difference in survival time (median 25 weeks) in all three treatment groups. Compared to Huber et al. [30], they applied a $^1/_3$ higher total radiation dose, but the overall survival time was not very different.

The Manchester Group [27] reported another large series of more than 300 treated patients, again without randomization between the different treatment protocols. They applied a dose range of 15–20 Gy with a single fraction. Although a large amount of the patients had only stage II or III disease, they were judged inoperable or not suitable for extensive EBRT. Therefore, median survival was better than in the other studies mentioned. However, it also reached only half a year for all patients. In accordance with Huber et al. [30], they observed longer median survival in patients with fatal massive hemorrhage as opposed to patients dying from local recurrences.

There is no valid recommendation for a single accepted dose/fractionation scheme. Considering the published data, irradiation doses of 15 Gy/fraction seem to approach the upper limits of tolerance of the bronchial mucosa. There are not many experimental data to support

Fig. 8–11. Before and 6 weeks after the completion of brachytherapy treatment. Despite increase in whole tumor mass, there is substantial decrease of the bronchial stenosis in the right mainstem bronchus. **8** CT scan before treatment. **9** CT scan after treatment. **10** Endoscopic view before treatment. **11** Endoscopic view after treatment.



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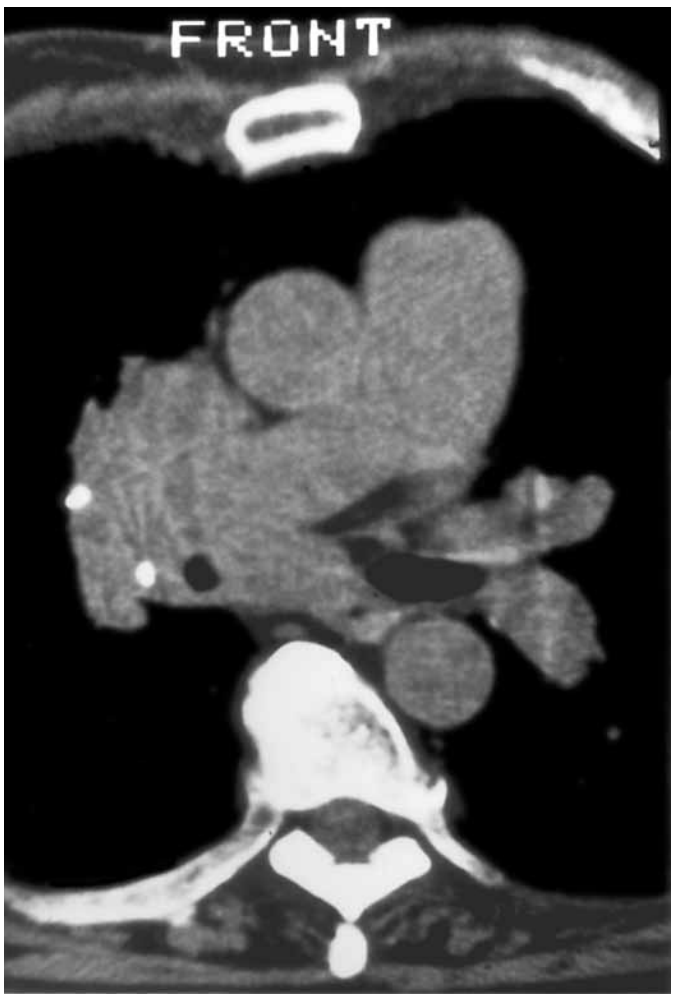

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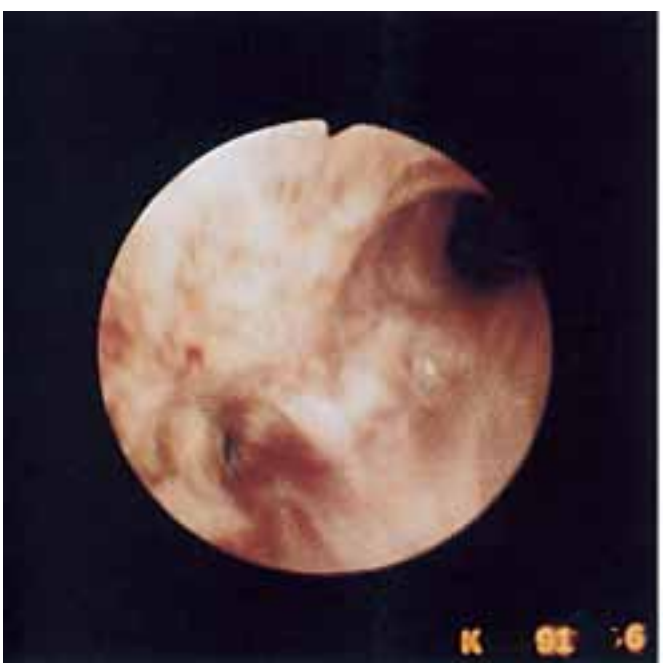

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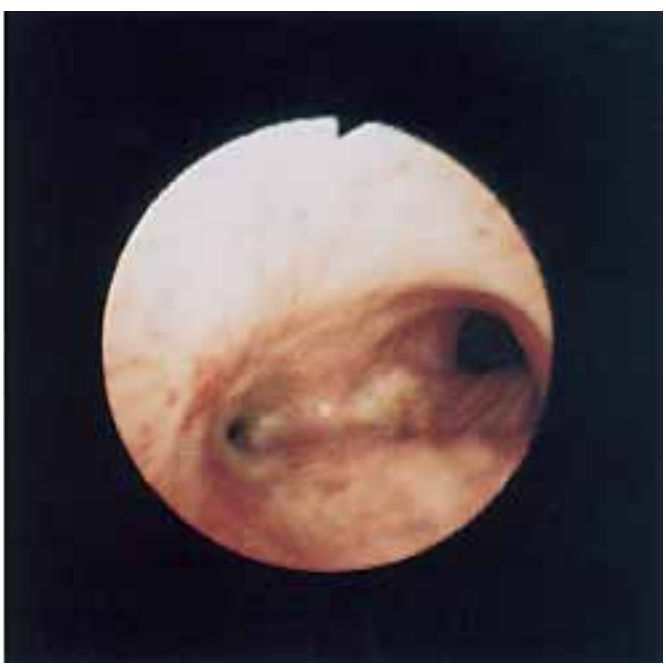

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Table 3. Example of a patient with adenoid-cystic carcinoma on the two mainstem bronchi pretreated with EBRT, electrocautery and Nd:YAG laser: improvement of lung function before and immediately after brachytherapy and 8 weeks later

Lung function parameter	Before therapy	Immediately after brachytherapy	8 weeks after brachytherapy
Vital capacity, liters	2.9	3.5	3.3
Peak expiratory flow, l/s	4.2	6.1	6.6
Total resistance, kPa/l/s	0.63	0.28	0.28
pO_2, mm Hg	75	82	88

this, however [41]. A higher total dose of more than 30–40 Gy seems not to be necessary to obtain sufficient local tumor control and is possibly associated with higher fatal hemorrhages [28].

We therefore recommend a regimen of 7–10 Gy (HDR) per fraction and a total of 2–3 fractions per treatment (fig. 8–11). This applies also to patients previously treated with EBRT. In patients treated previously with endoluminal brachytherapy, we believe that an interval of 6 months should be kept before initiating repeated brachytherapy.

Complications

Acute complications of the brachytherapy procedure are not more frequent than those occurring during routine diagnostic flexible bronchoscopy. The placement of the afterloading catheter and the following remote irradiation procedure are normally well tolerated. In LDR brachytherapy, the catheter is less well tolerated, therefore, the use of this treatment modality has significantly decreased.

As mentioned above, the brachytherapy procedure is usually not associated with severe morbidity or increased mortality, although patients with poor performance status are at higher risk.

The most important potential side effect of brachytherapy seems to be fatal hemoptysis. In some previous studies [18, 25, 28, 42–44] causes of death are shown. The occurrence of fatal hemoptysis is partly considered as a complication of treatment and not related to the disease itself. It is not clear if the incidence of fatal hemoptysis is related, for example, to tumor invasion into pulmonary vessels or related to the administered irradiation dose and fractionation regimen. The data on the natural course of lung cancer are sparse. Following Cox et al. [45], hemoptysis was the cause of death in lung cancer patients depending on the cell type in about 2–8% of all cases when external irradiation was applied. In a large series, the frequency of fatal bleedings was 3.3%, irrespective of treatment modality [46]. There was a correlation of this complication with squamous cell histology and tumor localization in mainstem bronchi. This localization represents a further negative selection towards more frequent hemorrhages. In the studies by Huber et al. [17, 30], the frequency of fatal bleeding from the tracheobronchial tree was 15% and accounted for a maximum 22% of all causes of death. Compared to other studies, the incidence of hemorrhage is higher, but this may be due to different selection criteria concerning localization and histology. For the interpretation of results, it should be kept in mind that most of the studies published are not randomized, not even prospective. In general, the incidence of fatal hemorrhage is high enough to strengthen all efforts to minimize potential side effects of endobronchial brachytherapy.

Postradiation bronchitis and stenosis can occur in a substantial number of patients undergoing endobronchial brachytherapy. Histological changes consist of mild mucosal inflammation to severe bronchial fibrosis. Speiser and Spratling [33] have proposed a grading system from grade 1 (mild mucosal inflammation, thin, circumferential membrane, no significant luminal obstruction) to grade 4 (greater degree of fibrosis with circumferential stenosis). Therapy of these postradiation effects consists of conventional treatment, such as inhaled steroids and antibiotics, or balloon dilatation, laser resection and stenting.

Overall, endobronchial brachytherapy must be considered a well tolerated, not very aggressive treatment option, especially in patients with reduced performance status.

Conclusion

Endoluminal HDR brachytherapy with Iridium-192 has a tumor-specific and long-lasting effect. Symptomatic improvement can be achieved in 70–80% of patients, and sometimes small tumors can be even cured by HDR brachytherapy. The afterloading procedure can be combined with all other modalities of tumor therapy. It can be used for example as 'boost' to conventional external irradiation and other local therapies, as local treatment modality in patients on systemic chemotherapy or as the only local treatment. Endoluminal brachytherapy is therefore a permanent interdisciplinary challenge with the need of a close contact between radiation oncologists and chest physicians.

However, the optimal dosage and fractionation schemes for the tumor therapy are still unknown, and there is need for further studies. Furthermore, in about 10% of the patients, radiation bronchitis occurs, and there may be fatal hemorrhage, often occuring weeks to months after the actual treatment. This complication could perhaps be avoided through better scheduling and dosing of the HDR brachytherapy.

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Therapeutic Bronchoscopy

Bolliger CT, Mathur PN (eds): Interventional Bronchoscopy.
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Photodynamic Therapy: Palliative and Curative Aspects

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Summary

Photodynamic therapy (PDT) is based on the interaction of tumor-selective photosensitizers and laser light. This interaction causes selective death of tumor cells. For palliative intention, PDT in comparison to Nd:YAG laser is approximately equally effective in relieving endobronchial obstruction by tumor. The time to treatment failure is slightly longer after PDT than after Nd:YAG laser resection, and the risk of reobstruction after PDT is lower than after Nd:YAG therapy. Additionally, PDT in most cases can be performed with flexible bronchoscopes and local anesthesia because there is no discomfort or significant risk during intervention. Compared to Nd:YAG laser recanalization PDT, however, has no immediate effect and therefore is not suitable for treatment of acute respiratory failure. For centrally located early lung cancers, treatment of incurative intention, the histologically confirmed complete remission rate 3 weeks after PDT is about 90%. However, over a long-term, only 50–70% of the patients remain stable. Therefore, PDT with curative intention does not achieve the success rates of surgical treatment with more than 80% and should be performed only in inoperable or high-risk patients. A main disadvantage of PDT is a prolonged photosensitization of skin and eyes. Strict protection from the sun is essential to avoid severe reactions. For patients, treated with palliative intention, with a mean survival of only 2–3 months, this means a severe reduction of quality of life. For patients with early-stage cancers treated with curative intention, the photosensitization of skin is less important in relation to the long mean survival time of these patients.

Photodynamic therapy (PDT) involves the administration of a tumor-localizing photosensitizing agent, followed by activation of the agent by light of a specific wavelength [1]. In vivo, PDT causes vascular shut-off with hypoxia and secondary tumor necrosis, while normal tissue is spared or suffers small damage that regenerates after PDT [2].

In its modern form, PDT has been studied for more than two decades, but has only recently been acknowledged as useful for a variety of malignant conditions.

The phenomenon of photosensitization, though, was already known at the beginning of the century.

In January 1998, the US Food and Drug Administration approved the use of Photofrin® (porfimer sodium) in PDT for patients with microinvasive lung cancer who are not eligible for surgery or radiotherapy [3]. Its use for palliation of certain cancers was approved in 1997. So far,

the approved indications for Photofrin and PDT (in the US) are: advanced-stage esophageal tumors, prophylactic treatment for papillary tumors (bladder), advanced non-small cell lung cancer and early-stage lung cancer. Approval is pending in: early-stage esophageal cancer, head and neck cancers, superficial bladder cancer, as adjuvant in brain tumors, head and neck cancers, intrathoracic tumors and intraperitoneal tumors [1].

Different types of tumors treated with PDT around the world include: malignant melanoma, angiosarcoma, squamous cell carcinoma, basal cell carcinoma, Kaposi sarcoma; brain tumors such as glioblastoma; palliation of esophageal carcinoma; retinal tumors including retinoblastoma and malignant melanoma; bladder carcinoma; vaginal, endometrial or cervical tumors; tumors of the tongue, nasopharynx, larynx and vocal cords, among others.

Its use in early-stage lung cancer is supported by several published studies, the most conspicuous was published by Cortese et al. [4], presenting PDT as an alternative to surgery. The complete response rate in early stage has been related to the size of the tumor, with a 97.8% success in tumor size less than 1 cm.

The procedure itself is relatively simple, generally performed under local anesthesia, and its technique is similar to standard fiberoptic bronchoscopy. Following the systemic administration of a photosensitizer such as Photofrin, a careful irradiation with the Argon-Dye laser is performed. This kind of laser produces a light of 630 nm wavelength, which is transmitted to the bronchial surface via a quartz fiber. The photosensitizer is then activated, and the resultant photochemical reaction destroys tumoral cells. Approximately 2 days after the treatment, a clean-up bronchoscopy is required to remove mucus and cellular debris usually too viscous for the patient to cough up. More than one session of clean-up bronchoscopies may be required to avoid complications such as infection, respiratory distress or respiratory failure [5].

Two types of fibers can be used for laser light delivery: for small superficial early bronchial cancers, surface illumination is usually achieved by a microlens fiber. For tumors parallel to the bronchoscope or involving smaller branches of the bronchial tree, a cylindrical diffuser is used. This type is also useful for large tumors, where the fiber is inserted into the tumor itself.

Current protocols use a power of 200–400 mW/cm^2 to deliver a total light dose of 100–200 J/cm^2 in a treatment time of 500 s [5].

Various kinds of lasers besides the Argon-Dye laser have been used so far: gold vapor laser, copper dye laser, excimer dye laser, diode laser and yttrium-aluminium-garnet (YAG) laser with a potassium titanyl phosphate crystal or an optical parametric oscillator [6]. The most widely used is the Argon-Dye.

Photosensitizers: A Little History

Most of the major developments in PDT history have taken place at the Mayo Clinic and Tokyo Medical College. In the early 60s, Lipson and Baldes reported the development of hematoporphyrin derivative, which did not have the adverse effects of hematoporphyrin. After that, they performed the localization of bronchogenic carcinoma using a mercury arc lamp, establishing the foundations of today's PDT. In the mid 70s, the first successful treatments of animal tumors were performed at Roswell Park Memorial Institute, utilizing a xenon arc lamp as a source of light. The introduction of laser equipment resulted in a rapid progress in PDT. At the beginning of the last decade, PDT was used to treat early-stage squamous cell carcinoma of the lung, and today more than 3,000 malignant tumors in various organs have been treated by this technique in 32 countries [6].

Porfimer Sodium (Photofrin)

This substance is the photosensitizer that has been studied most extensively. Photofrin and its predecessor, hematoporphyrin derivative, are both prepared from hematoporphyrin, and they are complex mixtures of oligomeric esters and ethers of hematoporphyrin. Early studies have demonstrated that they accumulate selectively and are retained longer by tumor cells or tumor tissue in comparison with normal surrounding tissues.

The tumoricidal capacity of PDT with porfimer sodium is limited by the maximum depth of penetration of light having a wavelength of 630 nm. This maximum wavelength has the power to penetrate tissue effectively up to 3–5 mm. Following the treatment, there is a period of skin photosensitivity that may last up to 6 weeks; patients must be advised to avoid excessive exposure to sunlight during this period of time [7].

Benzoporphyrin Derivative

Benzophorphyrin derivative is a second generation photosensitizer. It is a hydrophobic molecule, with a maximum absorption peak at 690 nm. Since this wavelength is above the absorption peak of hemoglobin, light is not significantly attenuated by blood or erythrocytes, and its penetration is maximal. Another advantage is its very rap-

id tumor accumulation, allowing optimal PDT 30–150 min after intravenous injection. It is rapidly cleared from the body, and skin photosensitivity does not extend beyond a few days [7].

Other Photosensitizers in Clinical Trials

Currently, some new photosensitizers can be found in stage II/III of clinical trials. Examples of those are: Tin Etiopurpurin, SnET2 (Purlytin); Lutetium Texaphyrin (Lu-Tex); Benzoporphyrin Derivative-Monoacid Ring A (BPD-MA); Tetra(*m*-hyroxyphenyl)chlorin, mTHPC (Foscan) and N-Aspartyl Chlorin e6 (NPe6) [1].

ALA-Based PDT

ALA (5-aminolevulenic acid)-induced endogenous photosensitization is a new approach to both PDT and tumor detection that utilizes the heme biosynthetic pathway to produce endogenous porphyrins, particularly protoporphyrin IX, an effective photosensitizer [1]. It has been used successfully to treat a large variety of superficial lesions (basal cell carcinoma, squamous cell carcinoma and adenocarcinoma). The residual photosensitivity after treatment has been reported to be 48 h. Probably ALA induces the protoporphyrin IX accumulation particularly in superficial mucosa such as the epidermis, conjunctiva, oral mucosa, vaginal mucosa, rectal, endometrial and ureteral mucosas. It also accumulates in glands, like the liver, sebaceous glands or mammary glands. In contrast, mesodermal tissue does not develop significant fluorescence after ALA injection in vivo although in vitro different results are found. The ALA-induced porphyrin fluorescence can be used in detection of lesions of the urinary bladder, early-stage lung carcinoma and malignant glioma.

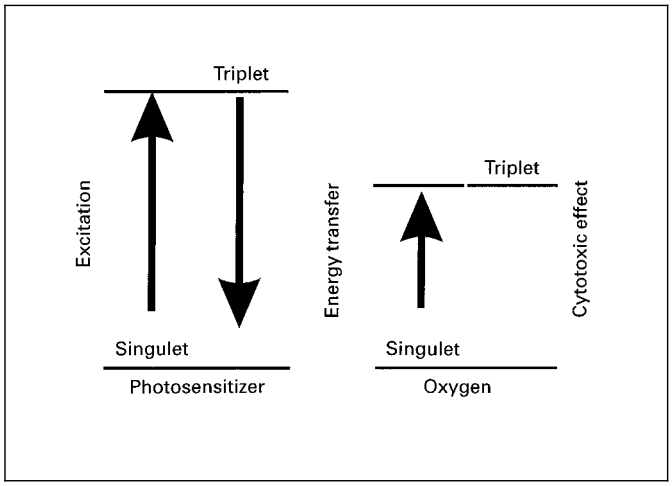

Fig. 1. Schematic explanation for the phototoxicity of a photosensitizer. With light of appropriate wavelength (e.g. 630 nm), the photosensitizers can be excited to triplet state. Energy transfer to oxygen produces singlet oxygen which is highly reactive and finally causes cell death.

Mechanism of Action

The mechanism of action involves the activation of the photosensitive molecule by light of specific wavelengths, with the subsequent creation of a variety of active forms of oxygen, the principal one being singlet oxygen. This formation of singlet oxygen in cell membranes, cytoplasm or organelles results in peroxidative reactions that cause cell damage and cell death. Photosensitizers used in clinical and experimental trials have the property to accumulate somewhat selectively in abnormal or proliferative cells, such as cancer cells or cancerous tissue; photoactivation produces effective ablation of the targeted tissue [7].

After the intravenous injection of hematoporphyrin derivative this substance can be found in the liver, spleen, kidneys, bone marrow and tumoral tissues. Normal organs eliminate the hematoporphyrin derivative quickly; tumoral cells, in contrast, keep the substance for more than 48 h.

The whole process of destruction is a very complex one and not completely understood. Basically, the damage to subcellular targets is related to the localization of the photosensitizer, given that the oxygen radical has a limited migration from the site of its formation. Photofrin accumulates in mitochondria, and its activation produces apoptosis. Other sensitizers are specific for organelles: lysyl chlorin p6 accumulates in lysosomas, monocationic porphyrin in membranes; their activation will produce cellular necrosis. The PDT damage to the plasma membranes can be observed within minutes after light exposure: swelling, bleb formation, shedding of vesicles containing enzymes, reduction of active transport, depolarization of the plasma membrane, increased uptake of the photosensitizer, increased permeability to chromate, inhibition of the ATPase [1].

Tumoral destruction: The targets of PDT include tumor cells, the microvasculature and the inflammatory and immune host system. The destruction of tumoral masses is based on three facts: (1) after being injected intravenously, the photosensitizer disseminates to all cells; (2) due to differences in vascular and lymphatic clearance from tumors and retention of the photosensitizer by

Table 1. Therapeutic response rates of Photofrin PDT and Nd:YAG treatment: US study (P17), European study (P503)

	US study (P17)		European study (P503)	
	Photofrin %	Nd:YAG %	Photofrin %	Nd:YAG %
n	33	37	69	72
CR + PR week 1	45	51	65	61
CR + PR month 1	42	19	61	36

CR = Complete response: absence of endoscopically visible tumor; PR = partial response: relative increase of ≥ 50% from baseline in the smallest luminal diameter or a decrease of ≥ 50% in the endobronchial obstruction.

tumoral cells, the photosensitizer is selectively retained in the tumor cells and interstitial tissue of the tumor, so that after 2 days there is a greater concentration of the photosensitizer in the tumor than in the surrounding tissue; (3) the photosensitizer will absorb light energy, and produce singlet oxygen, which destroys the tumor [7]. This reaction is known as photodynamic reaction, and is the main responsible of the tumor destruction (fig. 1).

Some other events are coming into focus, such as antitumor activity of inflammatory cells and tumor-sensitized immune reaction.

Both can be elicited by the phototoxic damage [7], and contribute to a more complete tumoral cell destruction.

Some factors can limit the direct tumor cell kill, such as an inhomogeneous photosensitizer distribution within the tumor and the availability of oxygen.

The application of some drugs can also affect the overall result of PDT treatment. Two drugs are known to modify the PDT response: adriamycin [8] and glucocorticoids [9, 10]. Both improve the effects of the therapy; the glucocorticoids increase the area of tumoral necrosis when administered 24 h after photoradiation.

PDT: Palliation of Lung Cancer

More than 50% of patients with nonsurgical lung cancer die from local complications such as asphyxia, hemoptysis, pneumonia, empyema. Publications state that 36% of patients died from similar causes, regardless of the presence or absence of prior surgery. A same cause of death in 58% of patients with surgery versus 83% of patients without was reported in another study [11]. Considering that only 30% of patients with bronchogenic carcinoma are surgical candidates at the time of diagnosis, it can be assumed that most inoperable patients will require palliative therapy at some point during the clinical course of the disease.

However, the use of PDT as a palliative treatment for patients with inoperable obstructive bronchial cancers must be assessed in the context of what may be achieved with conventional treatments. In the Nd:YAG laser therapy, the laser is used to coagulate and remove tumoral tissue. The treatment is usually delivered under general anesthesia and is highly effective in relieving airway obstruction, especially in tumors centrally located. Fatal hemorrhage, respiratory failure or cardiac arrest are severe complications of this treatment, but the incidence is very low (1.5%) and nonfatal complications occur in less than 0.5% of the cases [12]. Laser therapy is considered by many experts the gold standard for the palliative treatment of partially or totally obstructing, centrally located tumors of the airways, primary or metastatic.

There is plenty of published clinical experience to support this concept [12, 13]. Nonetheless, PDT is a useful palliative method that can have some advantages over laser therapy, particularly in tumors which are more peripherally located. Also, a more complete tumoral destruction and a better survival have been reported in many studies comparing laser photoresection versus PDT. Let us analyze some published reports.

Clinical Data

Two prospective, randomized trials of PDT versus Nd:YAG laser ablation for partially obstructive lung cancer have been reported [14]. These included data from 16 centers in Europe and 20 centers in the US and Canada. In the European trial, 40% of the patients had prior treatment, while all patients in the US and Canada had prior therapy. Tumor response was similar for both therapies at 1 week; but at 1 month 61 and 42% of the PDT patients showed sustained response in the European and US/Canada trials, respectively, whereas for the Nd:YAG group, the respective numbers were 36 and 19% only (table 1).

There were 12 and 6% of PDT patients versus 3 and 5% of Nd:YAG patients who achieved complete, biopsy-proven response in the European and US/Canada trials, respectively. Improvement in dyspnea and cough were superior for PDT over Nd:YAG in the European group, but similar in the US/Canada group. It was concluded that PDT is superior to Nd:YAG for relief of dyspnea, cough and hemoptysis [14]. Overall, adverse reactions were similar in both groups and 20% of patients in the

PDT group had photosensitivity reaction due to noncompliance with precautions [1].

A recently published prospective 14-year study [15] reported the evolution of 175 patients with primary endobronchial or tracheal squamous cell carcinoma or adenocarcinoma. Patients had failed, refused or were ineligible for conventional treatment. The results showed that survival was most significantly affected by the stage of the disease. When compared with other treatment regimens (surgery and radiotherapy), survival results were as presented in table 2 (modified from McCaughan and Williams [15]).

Analysis of the time after treatment required for reobstruction of the bronchus after YAG laser versus PDT showed that the immediate results were better after YAG laser treatment, but after the clean-up bronchoscopy, the degree of obstruction was the same, and the sites treated reobstructed faster after Nd:YAG laser therapy (2 weeks for YAG, 4 weeks for PDT).

A randomized study in the US comparing the efficacy and safety of PDT versus Nd:YAG laser showed that both treatments were equally effective in relieving endobronchial obstruction by tumor. The time to treatment failure was slightly longer after PDT than after Nd:YAG laser resection, and the risk of local recurrence after PDT was only 0.3 of that after Nd:YAG [16].

Another prospective trial of PDT plus radiotherapy, versus radiotherapy alone presented 41 patients. Results showed that the obstructive airway was completely open in only 10% of the patients treated only with radiotherapy versus 70% of patients when the combination was used. Twenty percent of patients failed with either treatment [17].

A group of 10 patients with inoperable non-small cell carcinoma presenting different degrees of tracheobronchial obstruction (86 ± 2%) showed a >50% response in 4 and <50% response in 6 patients, respectively. However, in all patients symptoms improved, especially coughing. Side effects included burns in 2 patients and mild anasarca in 1 [18].

Our own experience with 31 patients suffering from inoperable non-small cell cancer with variable degree of obstruction yielded similar results. We prospectively randomized patients to receive either PDT or Nd:YAG laser, finding that the immediate response was better in the Nd:YAG laser group, but the duration of the response was more prolonged in the PDT group, with a better survival rate. The number of complete biopsy-proven responses was low and short in duration. Palliation of symptoms as well as Karnofsky index was similar in both groups. The PDT group had a higher incidence of severe side effects, photosensitivity being the most important one [Diaz-Jiménez et al., unpubl. data].

Table 2. Comparative survival rates for PDT, surgery and radiotherapy

Clinical stage	Surgery months	Radiation months	PDT (KPS > 50) months	PDT (KPS < 50) months
I	42	19	not reached	NA
II	17.5	18	22.5	NA
IIIA	12	12	8	2
IIIB	7.5	10	7	4
IV	5	–	7	3

KPS = Karnofsky Performance Status; NA = not applicable.

Indications and Contraindications for PDT

Indications for PDT

(1) Relief of neoplastic endobronchial obstruction [1, 14–21]; (2) delay of tumor progression and improvement of symptoms [1, 14–16]; (3) making inoperable patients operable in selected cases [18, 20–22].

Complications of PDT

(1) Dyspnea, worsening obstruction due to edema, mucus plugs or atelectasis; respiratory insufficiency; (2) fever (reported incidence 20%); (3) infections: bronchitis, postobstructive pneumonia, due to edema and impaired cough mechanisms; (4) fatal hemoptysis; (5) photosensitivity; (6) allergic or toxic reaction to the photosensitizer.

Contraindications for PDT

(1) Tracheal lesions, carinal lesions, pneumonectomized patients; the edema resulting from the treatment can trigger respiratory insufficiency; (2) erosion or invasion of vascular structures; (3) porphyry or porphyrin hypersensitivity.

PDT: Curative Treatment of Superficial Endobronchial Tumors

Patients with central lung cancer have limited treatment options and poor prognosis. Many of these patients have chronic obstructive pulmonary disease or coexisting

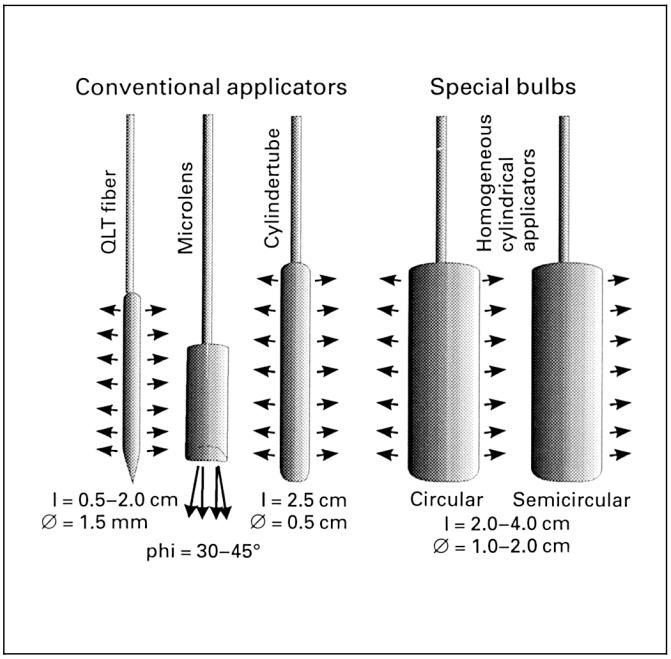

Fig. 2. Different forms of applicators used for curative PDT.

Table 3. Results of PDT in early lung cancer

Maximum dimension	Lesions	CR
Superficial type (123 lesions in 110 patients)		
<0.5 cm	64	61 (95)
<1.0 cm	25	22 (88)
<2.0 cm	20	9 (45)
>2.0 cm	14	6 (43)
Nodular type (45 nodular cancers in 43 patients)		
<0.5 cm	29	27 (93)
<1.0 cm	9	6 (67)
>1.0 cm	7	1 (14)

Figures in parentheses are percentages. CR = Histologically confirmed complete remission.

cardiovascular diseases. Surgery and high-dose radiotherapy are the standard therapeutic options for early-stage lung cancer either primary or recurrent. Even though early-stage endobronchial tumors are small by definition, a lobectomy is required in approximately 70% of cases. In the remaining 30% bilobectomy or pneumonectomy is required [23]. Often the reasons for which a patient is inoperable also preclude the use of radiotherapy. In patients with reduced pulmonary reserve, radiotherapy may further compromise lung function due to pneumonitis and fibrosis [24]. Because of the limited pulmonary function in many patients with lung cancer and the frequency of second primary cancer [25, 26] a treatment that will minimize loss of lung tissue is clearly desirable. Patients who cannot be treated with surgery or radiotherapy are limited to experimental treatments such as chemotherapy or immunotherapy or endobronchial treatment modalities such as endobronchial brachytherapy, cryotherapy or photodynamic therapy. PDT offers a potentially effective, minimally invasive treatment option and has been shown to be effective in selected patients with early-stage non-small cell lung cancer. The advantage of PDT over other forms of curative treatment of malignant tumors, e.g. surgery or radiation therapy lies in its selectivity. Therefore, treatment does not cause any loss of function. Its radicality, however, will remain a controversal issue in spite of the great number of studies [26–35, 42–44] that have already been published. Study designs varied greatly, a comparison of the results therefore is problematic.

For treatment a laser with 630 nm emission light, 2 W output power and specific light applicators according to the irradiated tumor area are necessary (fig. 2).

The total dose should be 200 J/cm^2. The irradiation time has to be calculated from the irradiated area and total output light power of the applicator (typically fixed to 400 mW).

Clinical Data

Phase I–II clinical trials in Japan by Hayata et al. [32, 33] showed that approximately 90% of superficial tumors less than 1 cm in diameter can be completely eradicated with PDT. Similar results were achieved in patients with nodular tumors less than 0.5 cm in diameter. Of 81 patients who had a complete response after PDT, only 2 had died from primary disease at the time of follow-up evaluation. Fifteen patients were still alive and disease free 5 years after treatment. Three patients were alive and disease free more than 10 years after treatment. The overall complete response rate after PDT was 71%.

A phase III clinical trial completed recently in Japan showed similar results. The complete remission (CR) rate, however, decreased significantly when treating larger lesions. Hayata [34] summarized the results using PDT to treat 168 early-stage cancers of the lung and esophagus in 150 patients, differentiating the lesions treated either into a superficial type or a nodular type (table 3).

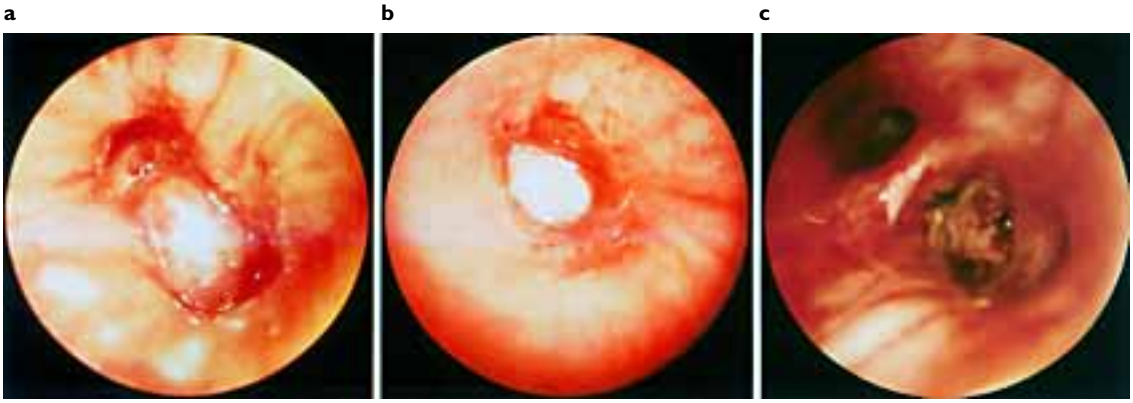

Fig. 3. a Squamous cell carcinoma obstructing bronchus intermedius – before PDT. **b** Three days after PDT – necrotic tissue after interstitial irradiation. **c** Three days after PDT – necrotic tissue after removal by forceps.

Table 4. Tumor characteristics and reasons for nonoperability

	n	%
Tumor characteristics (102 patients)		
Squamous cell carcinoma	87	85
T_{is}	23	23
T_1	63	62
T_2/T_3	8	8
Radiologically occult	90	88
Reasons for nonoperability		
Prior lung resection	48	47
Poor pulmonary function	43	42
Multilobar tumors	20	20
Central location	11	11
Old age	5	5
Refused surgery	4	4
Multiple reasons	61	60

Table 5. Response rate, survival and recurrence

Response rate, survival (100 patients)	
Total CR	79 (79%)
95% CI, %	71–87
Median survival, years	3.5
Median disease-specific survival, years	5.7
Tumor recurrence after first CR (79 patients)	
Recurrence	35 (44%)
Median TTR, years	2.8
Range, years	0.1–10.1

CR = Histologically confirmed complete remission; TTR = time to tumor recurrence.

Complete remission was achieved in 95% of the superficial type lesions less than 0.5 cm in diameter and in 88% of the lesions between 0.5 and 1.0 cm in diameter. The rate of CR decreased significantly in lesions larger than 1.0 cm in diameter. Recurrence developed in only 4 patients whose lesions had been less than 1.0 cm in diameter. Of the 83 CR cases treated with PDT alone, 3 patients died of the original tumor and 47 patients survived. Of these, 10 patients were disease free 5 years or longer after treatment.

In the lesions of the nodular type, CR was achieved in 93% of the lesions less than 0.5 cm in diameter and in 67% of the lesions between 0.5 and 1.0 cm in diameter. Of the 32 CR cases, 8 died of unrelated diseases and 23 patients survived. Of these 23 patients, 12 have survived 5 years or more.

Three open-labeled single arm studies which assessed the safety and efficacy of PDT with Photofrin were realized in Germany, France, the Netherlands and Canada. Their results led to the approval of the use of Photofrin in PDT for early superficial lung cancer in patients who are not eligible for surgery or radiotherapy [35]. A total of 102 patients were treated in these three trials. The indications were carcinoma in situ, microinvasive tumors not invading the cartilage by histological assessment and patients who were not considered candidates for surgery.

Figure 3 shows a typical example of PDT treatment.

Table 4 [35] presents the patient and tumor characteristics of the study population and reasons why these patients were not candidates for surgery.

Table 5 summarizes the overall results [35]. Histologically confirmed complete response was achieved in 79%

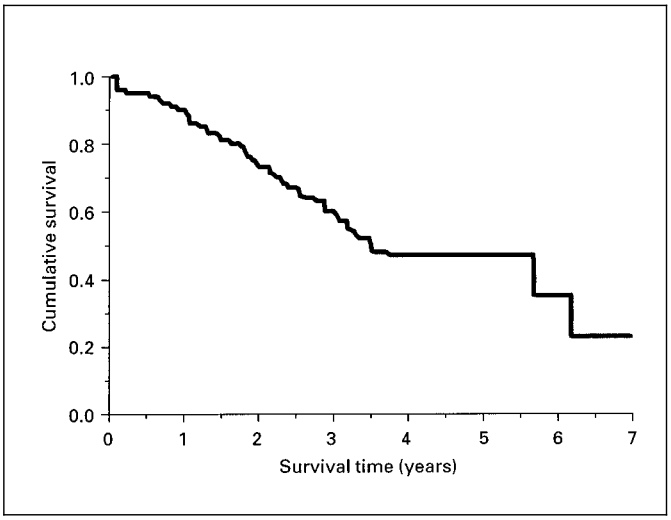

Fig. 4. Patient survival after PDT in superficial early lung cancer (n = 100 patients).

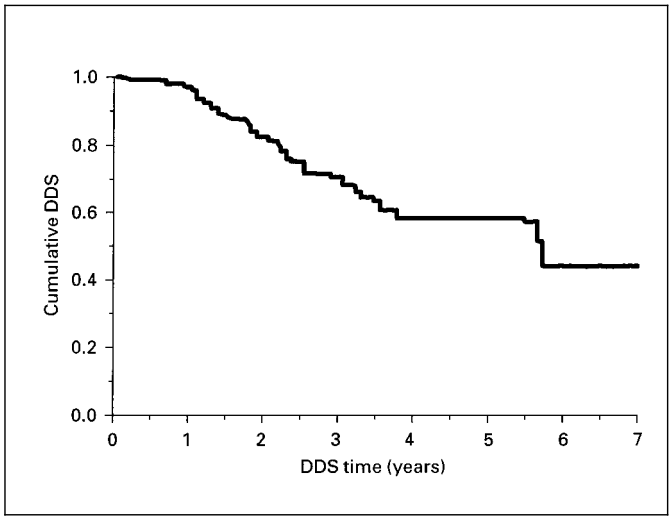

Fig. 5. Disease-specific survival (DDS) after PDT in early lung cancer (n = 79 patients).

Table 6. PDT in roentgenologically occult lung cancer: studies

Reference	Lesions	Response CR, %	Survival months
Monnier et al., 1990 [42]	16	69	3–60
Okunaka et al., 1991 [26]	27	98	mean 38
Edell and Cortese, 1992 [43]	14	71	7–49
Furuse et al., 1993 [30]	59	83	14–32
Imamura et al., 1994 [31]	39	64	4–169
Sutedja et al., 1994 [44]	39	72	2–95

CR = Histologically confirmed complete remission.

of patients with early-stage superficial nonsmall cell lung cancer (95% confidence interval 71–87%).

Median survival was 3.5 years (fig. 4) [35] and median disease specific survival was 5.7 years (fig. 5) [35].

These data were comparable to or better than those rates achieved with radiotherapy for stage I disease with complete response rate of 52–70%, a median survival of 72–48 months [36–40] and better than historic results of untreated patients [41]. The most frequent local adverse events were related to photosensitivity reactions (23%) which were usually mild to moderate sunburn-like reactions. Other adverse events included pulmonary effects related to the local pharmacological action of treatment which resulted in mucus exudate (23%), local edema (18%), stricture due to scars (10%) and ulcerations (9%). Perforations did not occur.

Table 6 summarizes the results of PDT in superficial endobronchial lung cancers of several studies which have been reported in the last decade. The numbers of the patients are low because these early lesions caused no symptoms and were mostly choice discoveries during routine bronchoscopies [26, 30, 31, 42–44].

In our center, PDT has been performed in 39 patients with 52 carcinomas including 47 invasive tumors and 5 CIS between April 1987 and July 1997. All lesions were radiologically occult and all patients deemed functionally or technically inoperable. In the immediate effect, we found a histology-proven curative rate of 92%. In the long-term follow-up (median time 25.7 months) 64% of these patients remained tumor free and 36% had a local relapse proven by endoscopic routine controls which were performed every 6 months. Finally, the overall cure rate was 59% [45]. The efficacy of preoperative PDT has been evaluated by Kato et al. [46]. A typical treatment of one of these patients is shown in figure 6. Tumors arising from an upper lobe bronchus or from the bronchus intermedius sometimes have superficial extension to the mainstem bronchus or lower trachea and therefore are either unresectable or would require pneumonectomy to remove. Following preoperative PDT, 4 of 5 patients with initially unresectable tumors were rendered operable and from 10

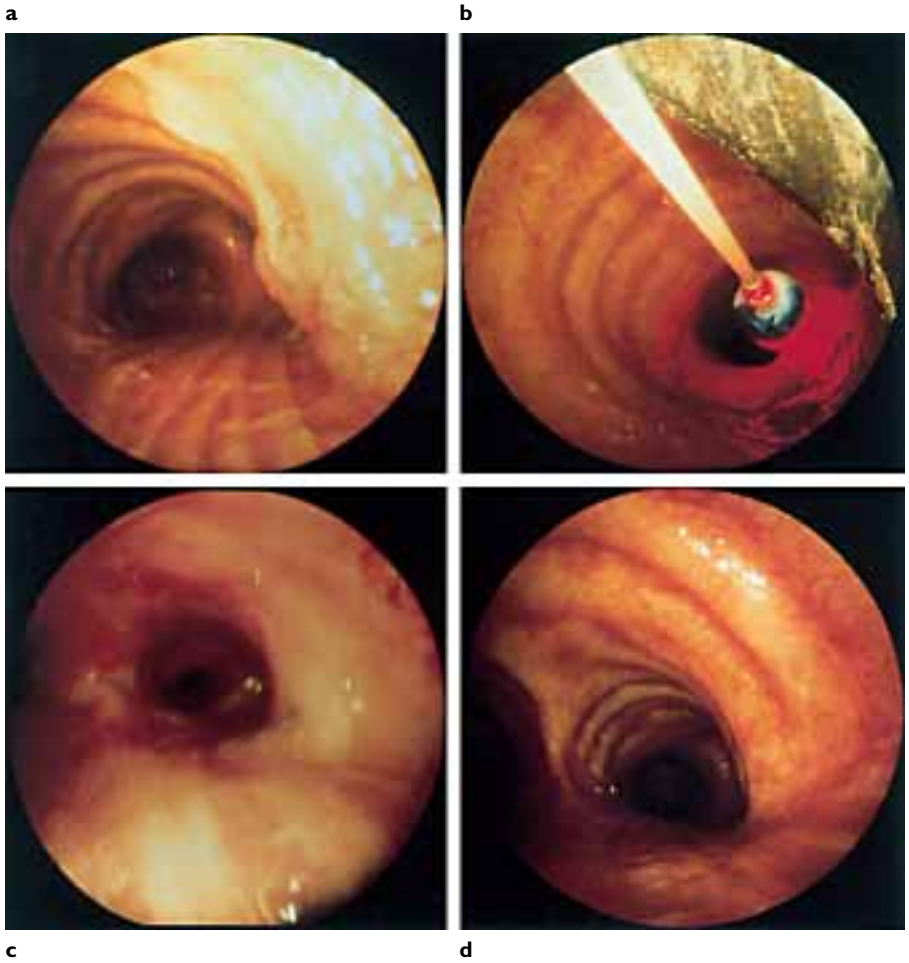

Fig. 6. **a** Squamous cell carcinoma in the right tracheobronchial wall, beginning of the right main stem bronchus – radiologically occult. **b** During irradiation with 200 J/cm^2 – direct contact of the irradiator with the tumor surface. **c** Three days after PDT: slight edema, thin fibrin plaque. **d** Long-term follow-up 5 years after PDT: Normal mucosa without any sign of local recurrence.

patients who were originally candidates for pneumonectomy, 7 became eligible for less extensive surgery.

Edell and Cortese [43] at the Mayo Clinic stated that PDT may be an alternative to surgery. In a preliminary study of 30 patients, a total of 14 cancers were identified and treated with PDT as first-line intervention. Complete eradication after PDT was achieved in 13 of 14 tumors (93%). Only 3 of the 13 had local recurrences at 7–18 months after PDT. Overall, 10 of the 13 cancers that showed a complete response have not recurred in up to 5 years of follow-up. In all, 10 of 13 patients (77%) were spared a surgical resection. Three patients with persistent disease after PDT underwent surgical resection and had surgical stage T1-N0-M0.

Conclusions

Palliative Treatment

PDT has proven to be effective in palliation. The first treatment with PDT was performed at the beginning of the 80s, since then the number of treatments has been increasing every day.

The clinical data available at the moment usually compare the effectiveness of PDT versus Nd:YAG laser therapy, which has been used for palliation since the 70s, and it is considered by some the gold standard in that matter. Both PDT and YAG laser resection are effective in relieving airway obstruction caused by intraluminal tumors. Nd:YAG laser photoresection seems to be better in tumors centrally located, where they are easily reached by the rigid bronchoscope, coagulated and then resected. PDT, on the other hand, is applied by flexible bronchoscope, which can reach tumors more peripherally located and does not require mechanical resection immediately

after the light irradiation. Repeated clean-up bronchoscopies, however, are needed some days after PDT treatment to remove detritus.

Since most patients with airway obstruction have a combination of intraluminal and submucosal or peribronchial tumor, it seems reasonable to use a combination of PDT and external radiation [17]. In very selected cases, PDT can also be used as palliative treatment for opening stenotic or obstructed bronchi due to tumor prior to the combination therapy with surgery [19, 46].

As a single treatment modality in patients with advanced disease presenting tracheobronchial obstruction, it seems that PDT still has a limited role given the availability of other treatment modalities, similarly or equally valid, particularly laser photoresection and brachytherapy, which are simpler to perform.

Additionally, some disadvantages have to be pointed out. PDT is not suitable for patients with tracheal lesions or lesions that compromise both main bronchus or pneumonectomized patients. The sometimes severe edema following the therapy can worsen the obstruction and make it complete, endangering life.

When the tumor has infiltrated the walls or vascular structures, the use of PDT can cause perforation and/or fatal hemorrhage.

Another disadvantage is that PDT does not immediately relieve the airway obstruction, and therefore, patients presenting with acute respiratory distress due to tumor obstruction are better treated with Nd:YAG laser resection.

Curative Treatment

For patients with central early-stage lung cancers, who are no candidates for external radiotherapy or surgery due to functional reasons, PDT offers a new and effective treatment modality with curative chance. In contrast to other unspecific local therapies, e.g. endobronchial brachytherapy, cryotherapy, electrocoagulation and laser coagulation by thermal effects, PDT is based on a selective death of tumor cells with subsequent necrosis of the irradiated tumor lesion. As all local methods, PDT is limited to centrally located lesions within the endoscopic view and to penetration depths of only some millimeters. The local tumoricidal effect of the above mentioned unspecific treatment modalities has been reported only in some few case reports. The curative effect of PDT in early superficial cancers, however, has been studied systematically and has been documented in several phase II and III studies. Since 1980, more than 800 patients have been treated.

The curative results of PDT range between 80 and 100% for the immediate effect (i.e. histologically confirmed complete remission within 3 weeks after PDT) and 50 and 60% for the long-term follow-up.

Main factors of influence are tumor size and penetration into depth. Successful application of PDT also depends on the ability to visualize the entire extent of the lesion bronchoscopically.

Informations about tumor geometry therefore are important. Autofluorescence bronchoscopy and bronchoscopic ultrasound have been developed for practical use recently and will be useful for assessing local tumor size and depth in roentgenologically occult lung cancer [47, 48]. In our experience, indication for PDT should be differentiated: CIS is an exclusive indication for a first-line intervention. Microinvasive carcinoma is an optional indication, treatment should be performed only in inoperable or high-risk patients. Invasive carcinoma is an indication for PDT only in highly selected inoperable patients with roentgenologically occult lesions which cannot be detected even by (high-resolution) CT scan. Severe dysplasia is not an indication for endoscopic intervention up to now.

One of the reasons for long-term failure is the high incidence for development of second primary tumors in lung cancer patients. Therefore, all patients treated should undergo regular bronchoscopy follow-up both for local control and exclusion of metachronous tumor lesions which could be treated by PDT too.

Photosensitivity is a main problem of PDT. The photosensitizing agent used in most clinical protocols is Photofrin, whose photosensitivity may last up to 3 months. Therefore, bronchoscopic intervention is limited to a period of 2 weeks after intravenous application of Photofrin, which must not be repeated within at least 2–3 months. The protection of eyes and skin is essential, and the patients must avoid exposure to light, particularly sunlight for a period of 4–8 weeks [49]. It is expected that with the second-generation photosensitizers, this will decrease considerably.

Developments, Future Aspects

A new field of investigation is concerning new generation photosensitizers with an improved tumor accumulation and a decreased photosensitivity of the skin. This might improve efficacy and decrease both local and general side effects of PDT.

Additionally, there is a need for better and cheaper light sources. Lasers might be replaced by conventional light sources with integrated filters for the emission of different wavelengths to obtain better penetration and a specific absorption of light by the sensitizer used. Additionally there is a need for better light delivery systems and light distributors. Thin flexible fibers should be used only in the smaller bronchi. Irradiation of more centrally located lesions should be performed by special light distributors adapted to the complex geometry of the bronchial tree to improve dosimetry. In summary, all these efforts could help to improve practicability, efficacy and safety of this newly developed treatment modality and to establish PDT in further clinical use.

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Tracheobronchial Stents

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Summary

Airway stents have been in use for almost 90 years. Today they are indicated for: (1) reestablishing patency of compressed or strictured central airways; (2) supporting weakened cartilages in cases of tracheobronchial malacia, and (3) sealing of fistulas and dehiscences to the esophagus or the pleural cavity. For benign stenoses, surgery remains the gold standard for the time being. Stent placement is the last option, and whenever possible a removable device should be inserted. In cases of malignant tumors, only polymer stents or covered metal stent may be used in order to prevent ingrowth of tumor tissue. Debulking and dilatation should always precede stent placement. Malacia is a relative indication for stent therapy. The results are less favorable. Sufficient sealing of fistulas to the esophagus, the mediastinum or the pleural cavity can be achieved with stents, though sometimes the commercially available models do not fit and they must be customized for a particular situation. Basically stents can be divided into four groups: (1) polymer stents such as the Dumon stent or the Polyflex stent; (2) metallic stents such as the Palmaz stent or the uncovered Wallstent; (3) covered metallic stents such as the covered Ultraflex stent and (4) hybrid stents such as the Dynamic stent. However, the response of the tissue and the outcome of the procedure depend more on the biomechanical properties of the prosthesis rather than the material used for its construction. Type, size and length of the stent must be carefully selected, considering the biomechanics of the airway obstruction and of the endoprosthesis and always considering the scenarios of possible complications. With all available stents granulation tissue formation may occur, the stents can get obstructed by incrusted secretions and all stents can migrate. Properly selected and used, airway stents are already an invaluable addition to the armamentarium of interventional bronchoscopy and chances are high that even better stents will be available in the foreseeable future.

About 100 years ago, the British dentist Charles R. Stent (1845–1901) invented a compound to cast dental models and splints. In the years to come, his name was used for various materials used to hold tissue in place or to provide support for a graft or anastomosis [1] . Today, surgeons and endoscopists insert stents into nearly all constricted tubular structures of the body, mainly to establish a sufficient lumen or to bridge a gap.

Historical Background

The implantation of an airway stent is by no means a recently developed procedure. Already in the last century, tubes had been surgically implanted by Trendelenburg [2] and Bond [3] for the treatment of airway strictures. In

1915, Brünings and Albrecht [4], disciples of Gustav Killian, the 'Father of bronchoscopy' implanted rubber prostheses endoscopically into narrowed tracheas. In 1933, Canfield and Norton [5] used a 'silver permanent dilating tube' to treat a 2-year-old child with bony stenosis of the larynx. This is the first documented implantation of a metal stent. Various alloys such as stainless steel, tantalum, titanium and recently nitinol have been tried since. Many of these stents had originally been developed for use in the vascular system, but were found to be adequate for implantation into the central airways after only minor modifications, if any at all.

The polymer silicone has been established as the most commonly used stent material. In 1965, Montgomery [6] designed a silicone rubber T tube, which involved an external side limb protrusion through a tracheostomy. These stents have been widely applied to manage subglottic stenoses of various origins. They are still used today with minor modifications by ENT surgeons. The first straight silicone stents without side limbs were inserted in 1965 by Anderson and Egnud [7]. The stents were inserted and fixed surgically after splitting the trachea. After insertion, the skin was closed without leaving a tracheostomy. The real breakthrough for silicone stent placement as an endoscopic measure came in 1990 when Dumon [8] presented a dedicated silicone stent for trachea and bronchi. These silastic stents became rapidly popular, and they are currently the most frequently used airway stents worldwide.

The first bifurcated airway prosthesis was developed by Neville et al. [9] in 1972. He used a bifurcated Dacron cuffed silastic device to replace intrathoracic trachea and stem bronchi. In 1980, Westaby et al. [10] reported the successful endoscopic insertion of a bifurcated rubber stent. While his stents still had a side limb, the bifurcated stents introduced by Clarke [11] in 1990 are held in place by their geometric shape and no longer require a tracheostomy. The anatomically shaped bifurcated Dynamic stent developed by Freitag et al. [12] in 1992 is a composite stent made from silicone with incorporated clasps of steel or nitinol.

At present, many companies and institutions work on 'better' stents. The latest developments include stents made of shape memory alloys and composite stents made from metals, polymers and textiles with optimized histocompatibility [13]. Further approaches are the developments of bioactive stents that will be integrated into the tissue and bioabsorbable stents [14].

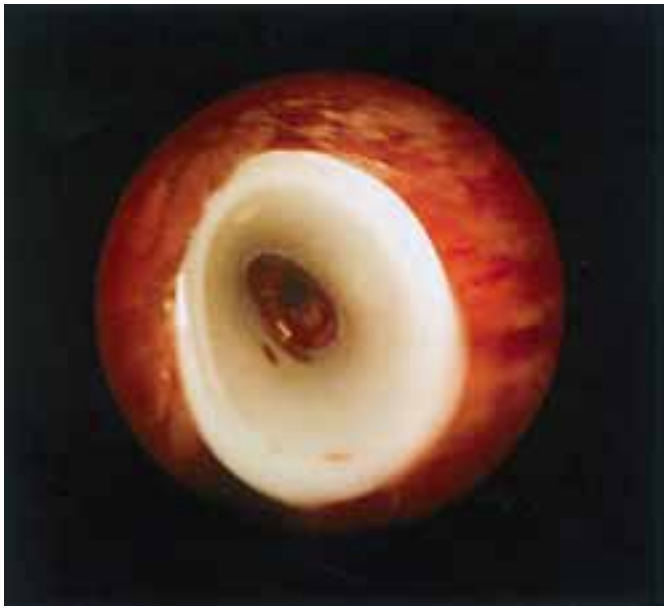

Fig. 1. Dumon stent reestablishing airway patency. Patient receives radiation therapy.

Indications

There are three major indications for tracheobronchial stents: (1) reestablishing patency of compressed or strictured central airways; (2) supporting weakened cartilages in cases of tracheobronchial malacia, and (3) sealing of fistulas and dehiscences to the esophagus or the pleural cavity.

Airway Stenoses

Airway stenoses can be classified according to their etiology (malignant or benign) or according to their shape and their biomechanical properties. The decision whether a patient is a better candidate for surgery or radiation therapy, laser or stent therapy can be very complex.

Malignant stenoses are hardly ever operable. However, as surgery is the only reliable way to eradicate a tumor, one should give this option a thorough consideration, even if an operation does not seem feasible at first sight. No stent can cure cancer. In most cases, intraluminally growing tumors can be removed endoscopically, e.g. by laser or cryotherapy. If a patient is short of breath and if the airway obstruction is dominantly due to extrinsic compression (by the tumor itself or by metastatic lymphnodes) a stent should be inserted. Malignant airway obstruction is the leading indication for airway stents in all

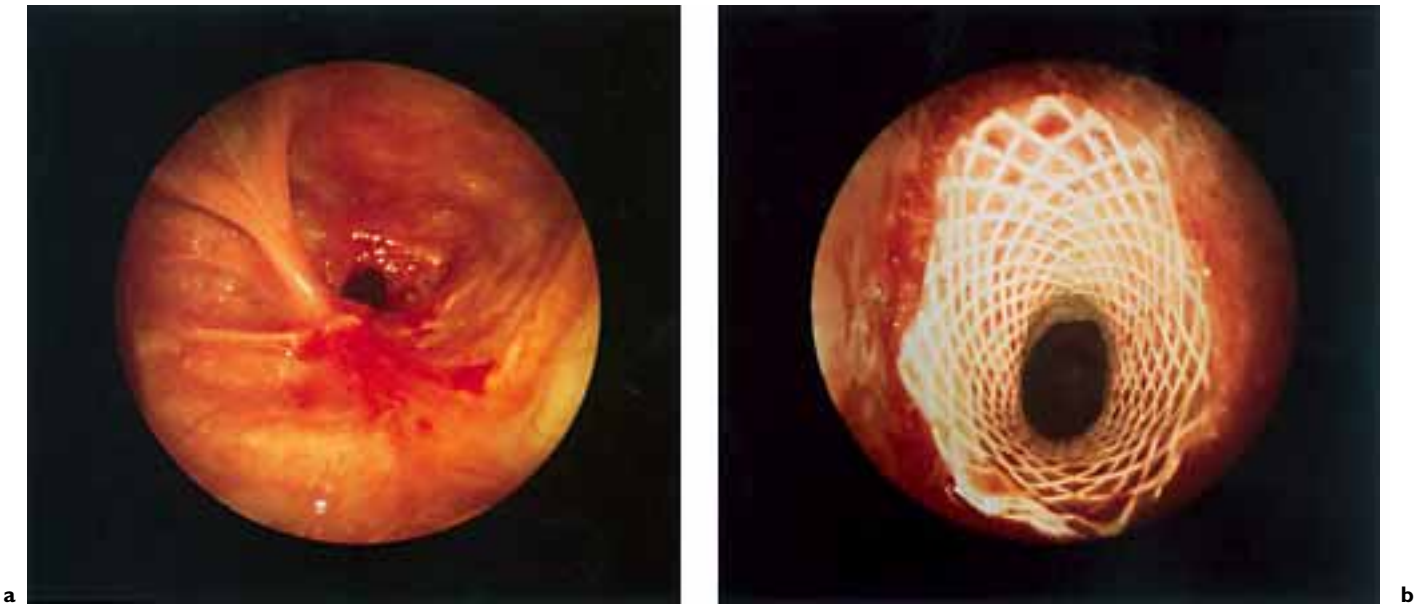

Fig. 2. a Benign tracheal stenosis following short time intubation after myocardial infarction. **b** Polyflex stent placed temporarily in the, at that time, functionally inoperable patient. Six weeks later the stent was removed and the patient received a tracheal sleeve resection.

larger studies [15–18]. However, stents should not only be regarded as palliative end-stage measures for terminally ill patients. Though a stent does not kill a single tumor cell, it can provide instant relief from dyspnea and thus can buy time for other treatments to take effect. With a stent in place, the patient can for example receive radiation therapy, brachytherapy or chemotherapy. If he responds sufficiently to these causal treatments, the stent can be removed.

Benign stenoses usually result from injuries to the mucosa with impairment of tracheal wall blood flow. Postintubation tracheal stenosis caused by high cuff pressures is still the commonest type of benign stenosis [19]. If a patient is symptomatic (dyspnea, stridor), endoscopic measures will be taken to reestablish airway patency. Dilatation of the scarred tissue is rarely long-lasting, and stent placement has emerged as the preferred type of treatment [20]. However, due to the high rate of complications in high tracheal strictures, a stent should only be placed if the patient is definitely inoperable [21]. A council with experienced surgeons should precede all stent therapies for benign diseases. For the time being, surgery (tracheal sleeve resection) remains the gold standard [22]. For high stenoses close to the vocal chords, a tracheostomy and a Montgomery T tube may be a safer alternative to surgery or to the insertion of indwelling stents. In cases of tracheobronchial strictures induced by radiation therapy, inflammation or impaired local blood supply (e.g. following bronchoplastic operation or transplantation), there is hardly any alternative to stent placement [23]. Shape and biomechanical behavior of the stenosis determine the treatment selection more than the nature of the underlying disease [24].

Malacia

The collapse of a major airway is caused by a structural abnormality of its wall. Basically, two forms of dyskinesia are found. In the 'scabbard trachea type', the cartilages are damaged resulting in lateral narrowing especially during a Valsalva maneuver. In the 'floppy membrane type', an unusually broad membranous part of the trachea bulges inward under forced expiration [24]. The later type is a common finding associated with lung emphysema. Patients suffer from dyspnea on exertion and retained secretions due to cough flow limitation. If breathing techniques (pursed lips) and standard therapies including CPAP or BIPAP fail, stent placement may be tried to stabilize the weakened airways [25]. Stents have also been used successfully for treating special forms of dyskinesia such as relapsing polychondritis [26] or tracheomegaly syndromes [27]. However, there are no reliable prognostic parameters, neither in pulmonary function tests nor in

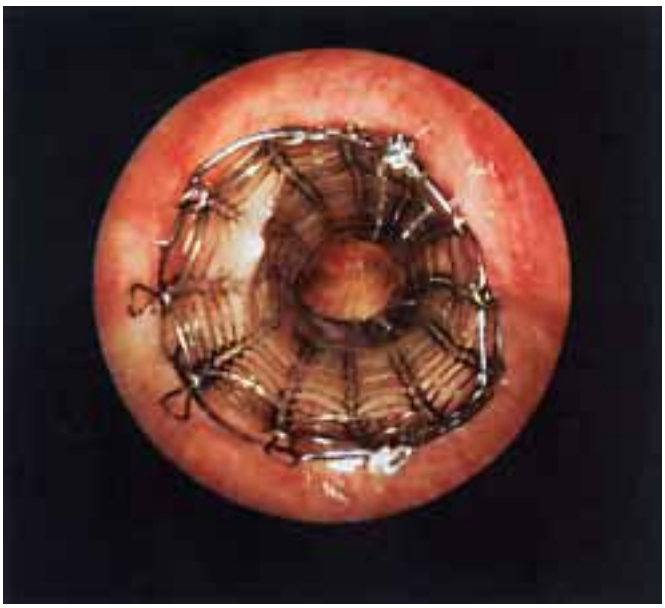

Fig. 3. Ultraflex stent stabilizing the weakened cartilages in tracheomalacia. Within the first 2 weeks, the stent can be removed, if the patient does not benefit from the procedure.

imaging techniques to predict whether a particular patient will benefit from stabilizing a localized dyskinesia. On the other hand, stent related complications (mucostasis, migration, granulation tissue formation) are more common in these patients. Because stent placement for malacia, especially in chronic obstructive pulmonary disease patients, remains a try and error maneuver, a removable stent should be selected.

Fistulas and Dehiscences

Fistulas between trachea or bronchi and esophagus can be congenital, but the majority is acquired through malignancies. A third of all esophageal carcinomas infiltrate the airways. The clinical signs of an esophagotracheal fistula are distressing cough associated with drinking and eating and aspiration pneumonia. Insertion of an esophageal tube often improves the quality of life, but usually fails to seal the fistula sufficiently. Double stenting with an esophageal stent and an airway stent yields the best clinical results and has become a standard procedure [28, 29]. We prefer to place both stents simultaneously under general anesthesia, often combined with the placement of a PEG catheter.

Stump fistulas or dehiscences are feared surgical complications of pneumonectomies in cases of central carcinomas and often consequences of R1 resections. Patients are lethally threatened by aspiration with exsudates from the pleural cavity. Common endoscopical sealing and bridging maneuvers include temporary intubation, the use of fibrin sealant, spongiosa blocks and the implantation of airway stents [30]. We have recently developed a technique of placing a spongiosa block and fixing it by placing customized stents. When the spongiosa gets organized, the stent can be removed.

There are numerous other stent indications. Stent might be used in cases of hemoptysis to control a bleeding site. They have been used to counteract airway compressions from enlarged or atypical vessels (aneurysm, sling complex). We have inserted stents to bridge huge defects and even complete dehiscences of the trachea in trauma patients. Stents are established devices in pulmonary medicine, otolaryngology and thoracic surgery. It is important to look upon them as aides and not as competitors to others methods for solving an airway problem in a critically ill patient.

Currently Used Stents

Specific Stents

A plethora of stents has been used in the airways. They can be divided into four major groups: (1) polymer stents such as the Dumon stents or the Polyflex stents, (2) metallic stents such as the Palmaz stent, the Gianturco stent or uncovered Wallstents, (3) covered metallic stents such as the covered Wallstent or the covered Ultraflex stent and (4) hybrid stents such as the Orlowski stent or the Dynamic stent.

Several other classifications or groupings might be used. Stents could be grouped by their major indication, their anatomical position, their insertion technique or whether they can be removed or not.

Many stents were used as investigation devices only and many have not passed the test of time. Only a very few stents have been approved by the FDA or the equivalent authorities in other countries. Figure 5 shows some stents that are currently used in our department. The first row displays polymer stents, the second row metallic stents, the third row bifurcation stents.

Straight Polymer Stents

T Tubes. The T tube, originally developed by Montgomery [6] in 1965, has undergone slight modifications. It is now distributed by several companies. Early models were made of acrylic, later replaced by a soft silicone rubber. T tubes are available in different diameters, fixed

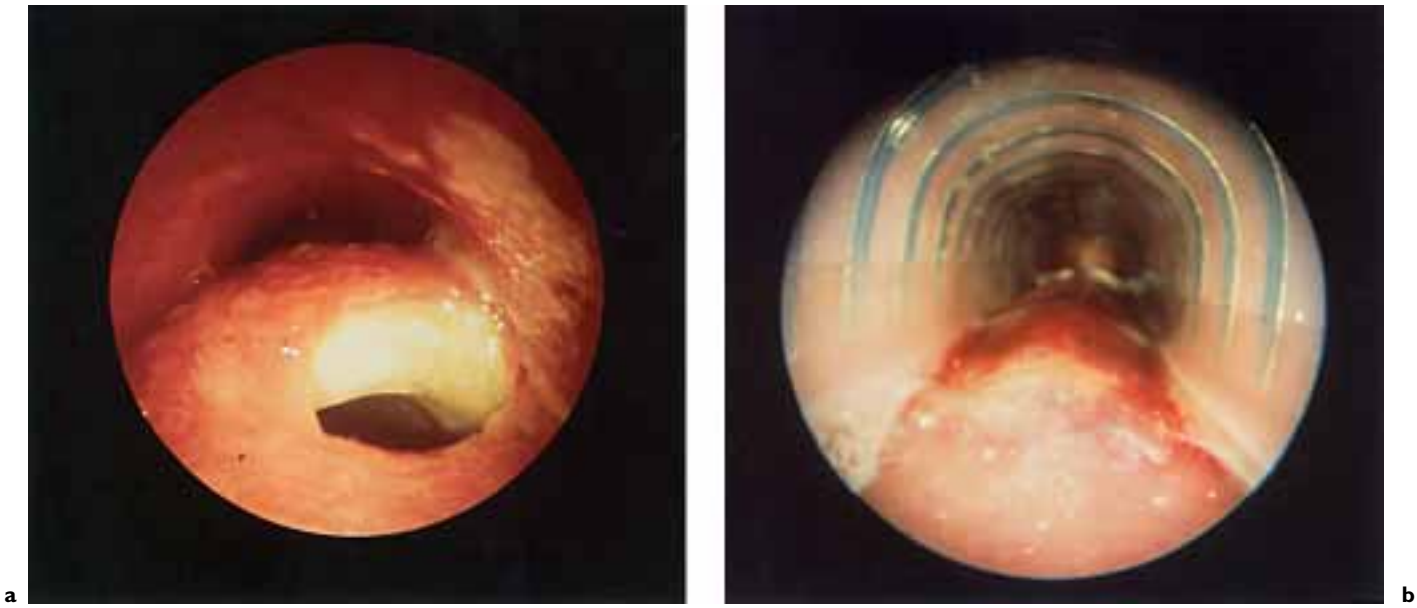

Fig. 4. a Huge esophagotracheal fistula from esophageal cancer. **b** Fistula sealed with a cuffed esophageal stent and a Dynamic tracheal stent.

and tapered and with various lengths of the three limbs (number 1 in fig. 5). They are used to treat tracheal stenoses at all levels up to the vocal cords. A Montgomery tube requires a surgical tracheotomy. The stent can be placed immediately in the same operation or after epithelialization of the tracheostoma. Later, it can be exchanged blindly or endoscopically. The limb coming out of the tracheostoma can be closed to enable speaking. It can be left open in cases of cricoid or glottic stenoses, or it can be unplugged temporarily to facilitate bronchial suctioning. Migration is nearly impossible, as one limb is fixed in the tracheostomy opening. An acute obstruction from dried secretions is the only dangerous complication. In contrast to all other stents, no high mucosal pressure is required to hold the stent in place. Consequently, blood and lymphatic flows of the sensitive upper part of the tracheal wall are not impaired. Thus, for the treatment of very high tracheal stenoses Montgomery T tubes are still the safest stents for the time being.

Orlowski Stents. Technically, Orlowski stents (Rüsch, Kernen, Germany) are modified Woodbridge or Tracheoflex tubes [31]. They have steel wire rings instead of a continuos coil, embedded in silicone (number 3 in fig. 5). Using a sharp scalpel, they can be cut to any desired length. Rings on the outer surface of the stent are intended to prevent migration. The tracheal stent is inexpensive, but it has too many disadvantages compared to other silicone prostheses available today.

Dumon Stents. Dumon stents (Novatech, Abayone, France) are the most frequently used stents worldwide. Within 10 years, they have become the de facto gold standard [8, 16]. Made from coated silicone with little studs on the outside, they look surprisingly simple. They are available in various lengths and diameters for the trachea and the bronchi (numbers 3 and 4 in fig. 5). The inner surface of a Dumon stent is very smooth. With the currently available models, problems with incrusted secretions are seen less frequently than in former years. Dumon stents are very versatile. They can be used for the treatment of any structural stenosis of the trachea, the stem bronchi or the bronchus intermedius of adults and children. For malacic stenoses, these stents are less suitable as their fixation depends on sufficient contact pressure between the airway wall and the studs. In flexible dyskinetic tracheas and in gradually opening benign stenoses, a Dumon stent is prone to migration. Many insertion techniques have been tried. Ideally, this stent is inserted through the Dumon-Efer bronchoscope using a dedicated pusher. If necessary, the stent can be repositioned, removed and replaced at any time with ease.

Polyflex Stents. The Polyflex stent (Rüsch) is a recently approved silicone stent with polyester mesh [32]. The

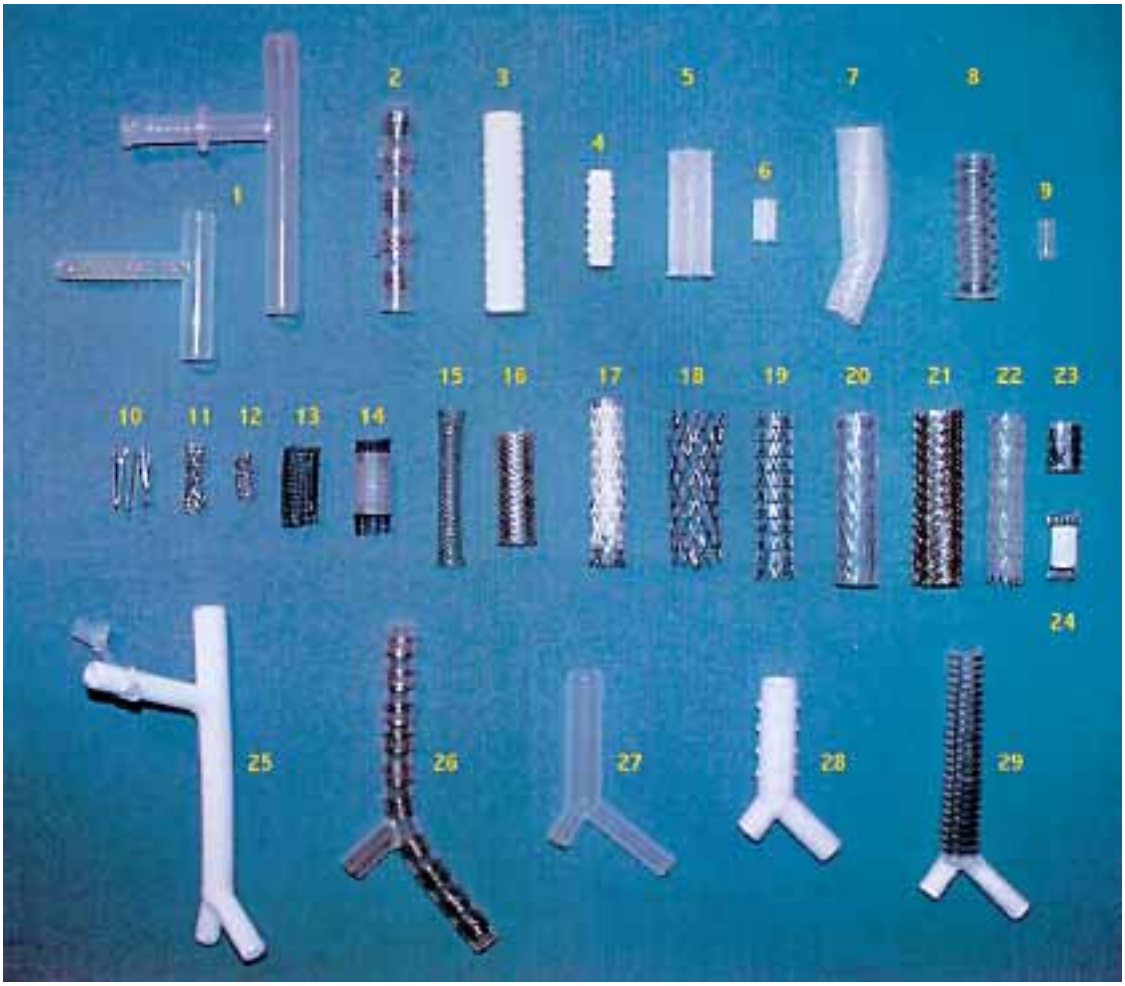

Fig. 5. Selection of currently used airway stents.

1. Montgomery T-tubes
2. Orlowski tracheal stent
3. Dumon tracheal stent
4. Dumon bronchial stent
5. Polyflex tracheal stent
6. Polyflex bronchial stent
7. Polyflex stump stent
8. Noppen tracheal stent
9. Hood bronchial stent
10. Gianturco stent
11. Palmaz stent
12. Tantalum Strecker stent
13. Uncovered Ultraflex stent
14. Covered Ultraflex stent
15. Uncovered Wallstent
16. Covered Wallstent

17–24. Prototypes of metal stents and compound stents currently tested preclinically and clinically

25. Westaby T-Y stent
26. Bifurcated Orlowski stent
27. Hood Y-stent
28. Bifurcated Dumon stent
29. Dynamic stent

hoop strength does not come from the silicone's elastic modulus, but from cross-woven polyester threads embedded in the silicone cover. The walls of Polyflex stents are thinner than the walls of Dumon stents or Noppen stents. Stent-in-stent placement (telescope technique) is possible with two Polyflex stents. In contrast to all other polymer stents, their circumferential length does not remain constant if they are locally compressed. Thus, they can adapt better to conical stenoses. The stent can be used to treat tumor stenoses as well as benign strictures of the trachea and the stem bronchi. It is also feasible to bridge esophagotracheal fistulas. Various lengths and diameters are available (numbers 5 and 6 in fig. 5). Special curved and tapered models are made on request for the sealing of stump fistulas (number 7 in fig. 5). Little tungsten spots in the stent wall make them visible on chest X-rays. As the outer surface of Polyflex stents is smoother than the surface of Noppen or Dumon stents, the risk of migration is slightly higher. A modification with silicone spikes on the outer surface for the prevention of migration has been

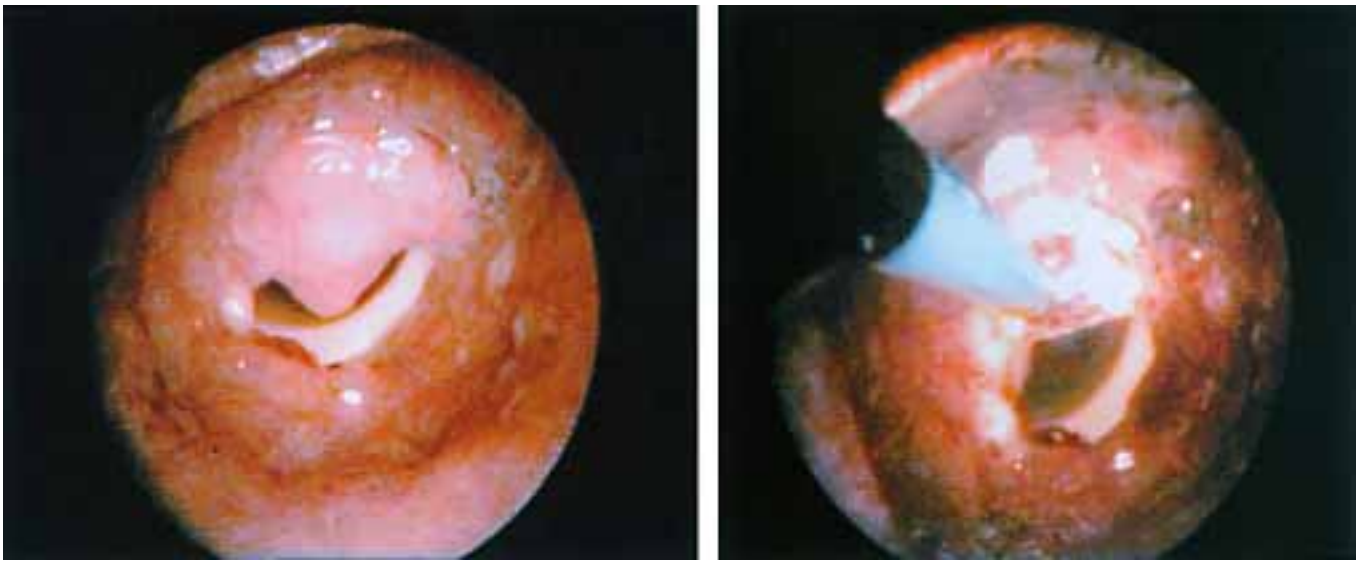

Fig. 6. Granulation tissue formation, causing a nearly complete obstruction of a stent in a high tracheal stenosis, is removed with the argon plasma coagulator.

tested in an animal model. However, the amount of granulation tissue formation was unacceptable [33]. Under circumferential compression (stricture) these stents show some foreshortening, under lateral compression (tumor), the lengths remain constant. The Polyflex stent should be placed with a dedicated introducer through a rigid bronchoscope or a Kleinsasser laryngoscope. Insertion, repositioning and removal procedures are relatively simple, provided there is good competence in rigid bronchoscopy with standard instruments.

Noppen Stents. Considerably different from the other polymer stents is the Tygon model (Reynders Medical Supplies, Lennik, Belgium) developed by Noppen [34]. Instead of studs like the Dumon stent, this prosthesis is thermally molded to have a screw-type outer surface which creates enough wall friction to hold the Tygon cylinder in place (number 8 in fig. 5). The stent is less elastic than other stents (fig. 6). A few years after its development, this screw-thread endoprosthesis, though less expensive, has not become very popular. A recent study comparing it with Dumon stents showed similar clinical results [35]. In this study, the Noppen stent had a lower migration rate in benign diseases. The indications for Noppen stents are similar to the indications for Dumon and Polyflex stents.

Hood stents. The Hood Company (Pembroke, Mass., USA), one of the market leaders in the USA, still offers little dumbbell-shaped silicone stents for bronchial anastomosis (number 9 in fig. 5). In Europe, these stents are hardly ever used.

Metal Stents

Gianturco Stents. Gianturco-Rösch stents (Cook, Bjaeverskov, Denmark), originally developed for blood vessels and the biliary tract, were frequently implanted into the tracheobronchial tree in the late 1980s [36, 37]. At that time, the Z wire stents were the only stents that could be inserted with a flexible bronchoscope [38]. The stent is made from stainless steel, expanding to 15 or 25 mm diameter (number 10 in fig. 5). Due to the barbs that embedded in the mucosa, migration did not occur. However, a few years ago, it became evident that the spring-type steel stent is too dangerous, giving rise to a high rate of airway wall perforation and granulation tissue formation [39–41]. The biomechanical behavior is unfavorable with high pinpoint pressure on the mucosa inclining the stent to destroy the tissue [42]. Furthermore, Gianturco stents showed a high rate of failures due to fatigue fractures. Today, with other metal stents available, placing Gianturco stents in the airways must be considered obsolete [41, 43]. Modifications of the original design may solve some of the problems [44].

Palmaz Stents. The Palmaz steel stent (Corning/Johnson & Johnson, Warren, N.J., USA) is a balloon-expandable mesh stent that has been developed for blood vessels and the biliary duct [45]. It has been used successfully in

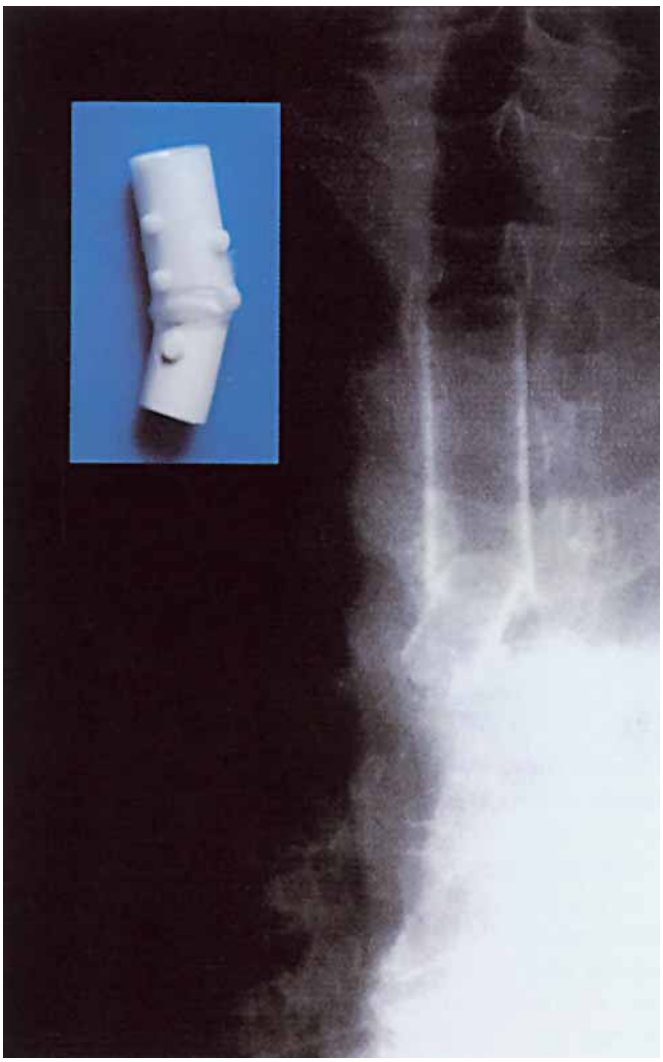

Fig. 7. A tracheal Dumon stent and a diagonally cut bronchial stent have been glued together to prevent tumor compression and invasion in the carinal region after pneumonectomy.

the airways [41, 46, 47]. Biliary stents with 18 or 30 mm nominal length and adjustable diameters ranging from 4 to 10 mm are feasible for lobar and segmental bronchi (number 11 in fig. 5). The stent can be adjusted in vivo to a desired shape with different angioplasty balloons or dilatation forceps. Thus, a tapered stent or a stent with steps, e.g. between lobar bronchus and bronchus intermedius can be modeled by the endoscopist. The stent is not covered, and it should therefore not be used in tumor-infiltrated areas. In benign stenoses, epithelialization is usually observed within a few weeks. Up to this phase, the stent can be repositioned or removed. The mechanical behavior of a Palmaz stent is more plastic than elastic. It is comparable to a copper cylinder. If the stent is compressed, it does not regain its shape and diameter after decompression. Pressure swings from coughing can irreversibly crush such a stent [42]. Therefore, Palmaz stents should only be used with extreme caution in the trachea or stem bronchi. The thin wall and the possible tailoring make it an ideal stent for smaller bonchi. However, one should seriously consider whether a stent in a smaller airway is prudent at all.

Ultraflex Strecker Stents. The Ultraflex stent (Microvasive-Boston Scientific, Natick, Mass., USA) made from Nitinol (number 13 in fig. 5) has replaced the former Strecker stent, which was made from tantalum [48] (number 12 in fig. 5). The knitted design permits axial and radial movements of the wire filaments. Thus, an Ultraflex stent can adapt well and smoothly to irregular shaped or kinked airways (fig. 3b) [15]. Recently covered (polyurethane) versions became available (number 14 in fig. 5). The bare stents are usually covered by epithelium within a few months. Beating cilia can be found inside the stent. The indications for Ultraflex stents are wide. They have been used for the treatment of tumor stenoses, benign stenoses and strictures. As the recoil (hoop strength) of the knitted Nitinol stent is not very high (fig. 7), sufficient predilatation, e.g. with angioplasty balloons or bougies, is required to accomplish good airway patency with this stent. The Ultraflex stent has also been used to seal airway fistulas to the esophagus or the pleural cavity. As the latest development, these stents are fixed on a semirigid catheter with the Crochet knotting technique. Using a guidewire, the stent can be placed with flexible endoscopes [49]. Repositioning and removal are far easier with rigid instruments. Granulation tissue formation at the end of the stents and tissue growth through the wire meshes has to be considered as with all metallic stents.

Wallstents. The Wallstent (formerly Schneider, Switzerland, now distributed by Boston Scientific) is a woven metallic prosthesis (number 15 in fig. 5). The stent is flexible and compressible and it can be bent without collapsing, unlike any other stent. The new model is surrounded by a layer of polyurethane, preventing tumoral regrowth through the metallic meshes [18] (number 16 in fig. 5). The stent can be used in the trachea or bronchi for the treatment of malignant and benign stenoses [50]. Due to its mechanical properties, the Wallstent is particularly useful for hourglass-shaped stenoses and for tapered regions of the bronchial tree such as the tracheal stem bronchus transition [51]. Sealing of a stump fistula after pneumonectomy can be achieved easily with this prosthesis. A

problem inherent to the design of the Wallstent is the foreshortening [42]. If it is compressed, circumferentially or laterally, it remains round shaped, but it becomes longer. Conversely, a slightly compressed Wallstent becomes shorter when it opens completely. This axial movement and spiking of the ends into the mucosa can stimulate granulation tissue formation [41]. The Wallstent can be placed with a dedicated rigid instrument, the Rigidstep device which is basically a 12 rigid bronchoscope or with a flexible catheter, the Telestep device.

Other Metal Stents. Several companies are developing new metallic stents. Nitinol is the most frequently used alloy because of its favorable biomechanics [42, 52–56]. Covered and uncovered versions are available as investigation devices (numbers 17–24 in fig. 5).

Bifurcated Stents

Westaby T-Y Tubes. A special T tube extending into the stem bronchi has been introduced by Westaby et al. [10] as the first bifurcated tracheobronchial prosthesis. Currently, the T-Y stent (number 25 in fig. 5) is available in three diameters from Hood. This stent is difficult to insert. The long, relatively rigid stent complicates coughing. Today, this prosthesis is only used for extremely long stenoses from the cricoid to the upper lobe bronchi.

Orlowski Y-Stent. Bifurcation models of the Orlowski tubes (number 25 in fig. 5) are available (Rüsch). They have been used for the treatment of extreme strictures [57]. Orlowski stents are inexpensive, but problems with retained secretions require frequent bronchoscopies. These Y stents have not become very popular, and in most countries they have been replaced by other bifurcated stents.

Hood Y-Stent. One of the best established stents is the bifurcated Hood stent (number 27 in fig. 5) [59]. It is softer than other bifurcated stents. The tracheal diameter is 14 mm, two lengths are available. Several techniques of insertion have been described [58]. Good skill in rigid bronchoscopy is required.

Dumon Y-Stent. The latest development in the Dumon stent series is a bifurcated model (number 28 in fig. 5). It is pushed blindly through the introducer system of the Efer bronchoscope. In the trachea, it has to be twisted and positioned with a grasping forceps until it sits on the carina. Compared to the straight cylindrical models it is far more difficult to insert. The stent can be removed like all other Dumon stents.

Dynamic Stents. Dynamic stents (Rüsch) are anatomically shaped, bifurcated silicone stents (number 29 in fig. 5) [12] They have a flexible posterior membrane, resembling the membranous part of the trachea (fig. 4). This membrane can bulge inwards during coughing, thereby increasing its efficiency. Due to this physiological functioning, problems with retained secretions are relatively rare. Dynamic stents are available in three sizes. They can be cut to the desired length. The stent has been widely used for the treatment of tumor compressions, strictures, malacias [17, 27], tracheobronchomegaly [59], and esophagotracheal fistulas [29]. Dynamic stents are superior for the treatment of long stenoses, involving two thirds of the trachea or the bifurcation. They can be inserted with a special forceps, an ordinary foreign body grasping forceps or, if necessary with flexible instruments [60–62]. Removal is possible without problems at any time.

Stent Selection and Insertion

Prior to stent placement, some preparations are necessary. Considering all the possible immediate and long-term complications, extreme caution is strongly advised. In the interest of the patient and an optimal outcome, a mental checklist should be worked up by the endoscopist before he goes to action.

1 Does this patient really need a stent?
2 Will he truly benefit from a stent?
3 Will stent placement interfere with or even prohibit a surgical procedure?
4 Is it safe to place a stent in this anatomical condition?
5 Is it safe that I place a stent with my expertise, my team, my equipment?
6 What is the type of stenosis or fistula? What kind of stent is ideal for this condition?
7 What length and diameter is needed?
8 Do I have the optimal stent at hand or shall I order a more appropriate one?

The stent should be selected according to the underlying disease, the anatomical situation and the foreseeable time course. In cases of benign strictures, a short removable stent is advisable in order to minimize the damage to the unaffected mucosa. Otherwise, a later surgical approach might be hindered. For a malacia, a stent should be used that has a low migration rate. A wire mesh stent without covering is usually preferable as it preserves sufficient humidity of the mucosa and to some degree even mucociliary clearance. On the other hand, tumor tissue or fast developing granulations would grow through the meshes of uncovered stents. Only polymer stents or covered metal stents should be used for these diseases. In

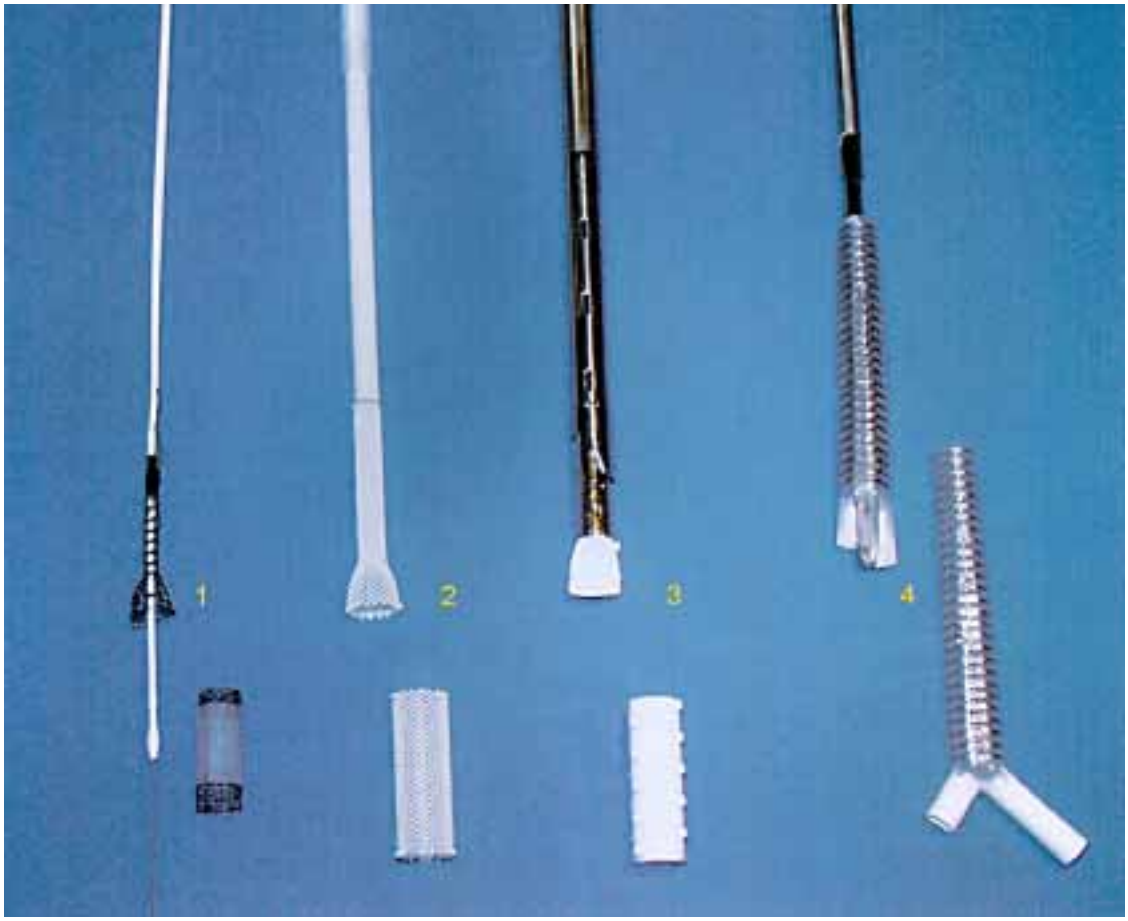

Fig. 8. Insertion and deployment devices for commonly used stents.
1. HTR delivery system for Ultraflex stents
2. Tube push system for Polyflex stent
3. Efer bronchoscope with Dumon stent
4. Dedicated forceps for insertion of Dynamic stent

malignant stenoses, a possible progression has to be considered. Tumor overgrowth at the stent edges might occur if the stent is too short in first place.

Insertion Techniques

Stent insertion ranges from a simple outpatient procedure [63] to highly sophisticated surgery using an extracorporal lung assist [64]. Most stents require rigid bronchoscopes for insertion and most authors agree that this is the fastest and safest approach [65]. Several techniques have been described for the insertion of silicone stents and metallic stents using flexible bronchoscopes under local anesthesia [49, 66–68]. Even if insertion is possible without rigid equipment, handling of possible complications is almost impossible without rigid bronchoscopes. Thus, for the time being, rigid bronchoscopy should be at least available anytime when stent insertion is planned.

Special catheters and deployment systems have been developed for the placement of metallic stents. The original Strecker stent (Boston Scientific) was mounted on a balloon catheter. Using the balloon, the stent was inflated and deployed in the stenotic area. The Gianturco stent (Cook) was pushed out of a catheter. Both stents did not pass the test of time.

The Ultraflex nitinol stent (Boston Scientific) is self-expanding. It is mounted on an introduction catheter with Crochet knots. Pulling on the thread gradually opens the knots and releases the stent [49]. Up and down reposition-

ing is possible until the stent is completely set free. Two models are available. The distal release option is easier to handle (number 1 in fig. 8).

Polymer stents are usually placed under general anesthesia [32]. The Polyflex stent is squeezed into an 8-mm tube which is then slipped through a rigid bronchoscope into the stenosis. While a pusher holds the stent in position, tube and bronchoscope are withdrawn until the stent is deployed (number 2 in fig. 8).

Standard bronchoscopes can be used, but some dedicated instruments have been developed to facilitate introduction and deployment of particular prostheses. Dumon stents are ideally inserted with the Dumon-Efer bronchoscopy set (number 3 in fig. 8). Exchangeable tubes can be used for dilatation until a sufficient lumen is achieved for the complete opening of the stent.

Dynamic and other bifurcated stents can be placed with a dedicated forceps or a normal forceps [60, 62] (number 4 in fig. 8). Using a guidewire and fluoroscopy can facilitate the implantation. If necessary, it is possible to insert such a prosthesis with flexible instruments under local anesthesia [61]. In some cases, it is preferable to use a bronchoscope with a lens in order to place a Dumon stent or a Dynamic stent under direct vision [41].

Dilatation

Sufficient dilatation is a prerequisite of stent insertion. Rigid bronchoscope, bougies or balloons can be used to dilate strictures. One should not underestimate the importance of this procedure. Tumor tissue should be removed first, e.g. with the Nd:YAG laser. The largest possible prosthesis should be selected. Even if a stent is not completely unfolded, it can usually be opened with a balloon or a forceps. As tissue has complex visco-elasto-plastic properties, it might take some time until the desired lumen is achieved [24]. In cases of benign strictures, a gradual dilatation effect can be observed, even weeks after stent placement. As a rule of thumb, the nominal stent diameter should be about half way between the diameter of the normal unaffected airway and the stances. A tracheal stent for example treating an 8-mm stricture of a normally 18-mm trachea should have a nominal diameter of 14 mm, provided that dilatation of 12 mm could be achieved prior to stent placement.

After stent placement, a stent pass should be given to the patient. The pass should provide all necessary information about the type and exact location of the stent. It should be stated clearly, whether an endotracheal intubation is possible with the stent in place and what size of endotracheal tube can be inserted in case of an emergency. A nebulizer should be prescribed. Adequate humidification is the most efficient countermeasure against retained secretions in the stent. A prescribed peak flow meter can help to indicate the need for an endoscopical intervention, e.g. to remove dried secretions or granulation tissue. Figure 8 shows insertion and deployment devices for commonly used stents.

Stent-Related Complications, Prevention and Management

Despite the many good things that can be accomplished with airway stents, one should not forget the many possible problems associated with these 'iatrogenic foreign bodies'.

Migration

The commonest complication with polymer stents is migration. Indwelling silicone stents are held in place by the pressure between their outer surface and the mucosa. Most stents have studs, rings or other protuberances to increase the friction. If a tumor shrinks, e.g. in response to radiation therapy, the contact pressure declines and the stent can migrate. Migration rates are higher in the trachea and higher in benign stenoses [16, 24, 35]. A benign stricture usually responds to the counteracting dilatation pressure of a stent in the same way as it does to a dilatation balloon. The cross-sectional area gradually increases, and the stent starts to migrate. The time scale is unpredictable. It depends on the severity of the damage, the amount and the content of the scar tissue. Some strictures open within hours while others are still contracted after months. Malacic stenoses should not be palliated with straight indwelling polymer stents in the first place. Whenever a stent is placed, the worst case scenario has to be considered. Type, size and position of the stent must be selected in such a manner that a possible migration could not block a larger airway.

Mucostasis

Under normal conditions less than 5 ml of mucus are produced per day. The thin mucus film is transported cephalically by ciliary beating. Excessive secretions (sputum) resulting from inflammation or irritation must be cleared by coughing. Obviously, there are no beating cilia inside polymer stents and covered metal stents. Eventually, ciliated epithelium grows between the wire meshes of certain metal stents. Small volumes of secretions can be adequately transported by these cilia [69]. Most often,

however, coughing is the only mechanism by which a stent patient can expel his or her sputum. Rigid stents and very long stents require a higher cough flow to create sufficient shear forces. Dynamic stents cause fewer problems. Cigarette smoking results in tar films on the stent surface. This tar acts as an adhesive to sputum, resulting in incrustations of secretions. Patients with stents should quit smoking. In the first days after stent placement, bronchial suctioning is often required. The best measure to prevent mucostasis in the long run is a regular inhalation with a simple mist inhaler (large water droplets). Excessive secretions can be avoided by treating concomitant infections and inflammations with antibiotics and topical steroids.

Stent Obstruction

Tumor tissue can easily grow through the openings of uncovered metal stents. Therefore, in cases of intraluminal malignant obstructions polymer stents or covered metal stents should be selected. Even if these stents are used, a tumor can grow over the edges and can sometimes protrude into the stent. To avoid this, it is important to select a stent which is long enough in the first place. If tissue penetrates the meshes of a wire stent, a highly efficient approach is by removing it mechanically and applying intraluminal radiation.

The constant friction of stents and high localized pressures on the mucosa promote the development of granulation tissue. A stent should fit tightly and should not move to avoid friction. On the other hand, it should not apply too much pressure, as this would impair the mucosal microcirculation. It is important to select the proper size of stent and to make sure that the stent ends are smooth. Especially at sharp edges of polymer stents and at the tips of wire stents, scarring is frequently found within days. Cut ends of polymer stents must be smoothed, e.g. by using a grinding tool. The region below the cricoid seems to be most sensitive. Indwelling stents in the very upper part of the trachea are critical. Usually a Montgomery T tube or a silver cannula are safer. Steroids usually fail to prevent growth of granulomas.

If a stent becomes occluded by tumor or granulation tissue, caution is required. Laser resection is not advisable, as most stents are inflammable. Ignition hazards and stent damage can be avoided by using other techniques such as cryotherapy or argon-beamer coagulation [70]. A recently developed semirigid argon-beamer catheter has proved to be feasible for cutting granulation tissue at the edge of metal and silicone stents (fig. 6). Internal or external radiation therapy is possible with any type of stent. Neither metallic stents nor polymer stents are affected by X-rays or γ-rays. Brachytherapy with 5–10 Gy through the stent can prevent further development of granulation tissue.

Mechanical Stent Failure

Airway stents are under permanent stress of varying degree and orientation. Constant tumor compression, rapid compression from coughs, respiratory motion with elongation, tossing and torque of the trachea create a complex pattern of stresses that can yield fatigue fractures of stents [42]. Newer alloys can resist more deformations, but for the time being a possible failure has to be considered with all available stents.

Embedding and Perforation

The most dangerous complication is the perforation of one side of the stent through weak tumor tissue. In this instance, the stent edge disappears in the destroyed airway, leaving even less space for ventilation than the patient would have without a stent [42]. The stent has to be removed and must be replaced by a longer model, e.g. by a bifurcation stent. An alternative might be a stent in stent placement (telescope technique).

Biomechanical Considerations and Stent Materials

Looking at the different indications, it becomes obvious that there are diverse biomechanical requirements. Stents should oppose the recoil of tracheobronchial stenoses. They should stabilize floppy airways as in tracheomalacia, but prevent airway collapse without being a trap for mucus. Sealing of an airway-esophageal fistula requires that the stent is tight and adapts well to the surface of the airway, preferably without altering airway mechanics. The inner stent surface has to be smooth to prevent incrustation of secretions. The outer surface, which is in permanent contact with the mucosa, must be highly biocompatible and nonirritating. The stent should be easy to insert, and should adapt well to the irregularly shaped airways. The stent should not migrate but be easy to remove. Various materials and constructions have been used to meet these requirements. The most often used materials for modern stents are silicone, polyurethane, Tygon, stainless steel and nitinol. Modern polymers are stable under most physiological conditions and bacteriologically indifferent. Today, most commercial stents, such as the Dumon stent, are made of silicone. The Polyflex stent is made from polyethylene threads embedded in silicone,

the Dynamic stent has steel clasps encased in silicone. Some metal stents are covered by polyurethane, which is softer and more stretchable. Noppen stents are made from Tygon.

Most vascular stents are made of stainless steel. Their recoil and elasticity is determined by their shape and construction rather than by the properties of the material itself. Balloon-expandable Palmaz steel stents can be dilated to a desired diameter. Their behavior is far more plastic than elastic. Thus, if they are severely compressed, e.g. by a cough, their shape is altered, they collapse and do not regain the desired luminal profile. Gianturco stents on the other hand, are made of the same stainless steel, but they are spring loaded, self-expanding, and their mechanical behavior is purely elastic [42]. Newer stents such as the Ultraflex stent are made from nitinol, an alloy with unique biomechanical properties. It is a shape-memory metal with superelasticity. Nitinol can be squeezed more than 'normal' metals without breaking or being permanently deformed. Thus, these stents can be mounted on or into very small catheters. This facilitates insertion with flexible endoscopes.

Recoil

Considering that all commercially available stents have basically the same indication (opposing the constringent force of a tumor), one would expect that they should have similar biomechanical properties. At least the tensile strength (expansion force) should be in the same range. We have tested many airway stents that are recommended for the treatment of malignant stenoses with a simple stress-strain testing apparatus resembling a tumor compression. The technique and the devices have been used before and are described in detail elsewhere [42]. Basically stents are compressed in 0.2-mm steps while the necessary force is measured with an electronic force transducer. Stress versus strain are plotted. Surprisingly the stress-strain curves of figure 9 show that the recoils of the popular airway stents differ by several orders of magnitude.

The results of these measurements indicate that the true constricting forces of airway tumors, benign stenoses or strictures are completely unknown. Selecting a stent with optimal mechanical features is currently based on assumptions and not on scientific data. We have developed an instrument to acquire in vivo stress-strain curves in stenotic areas through a bronchoscope. Unfortunately, practical problems such as fragility of the force transducers, disinfection or proper calibration have hindered the use in daily hospital practice. However, it is certainly important to know what biomechanical property is actually required in order to select the most appropriate stent for a given situation.

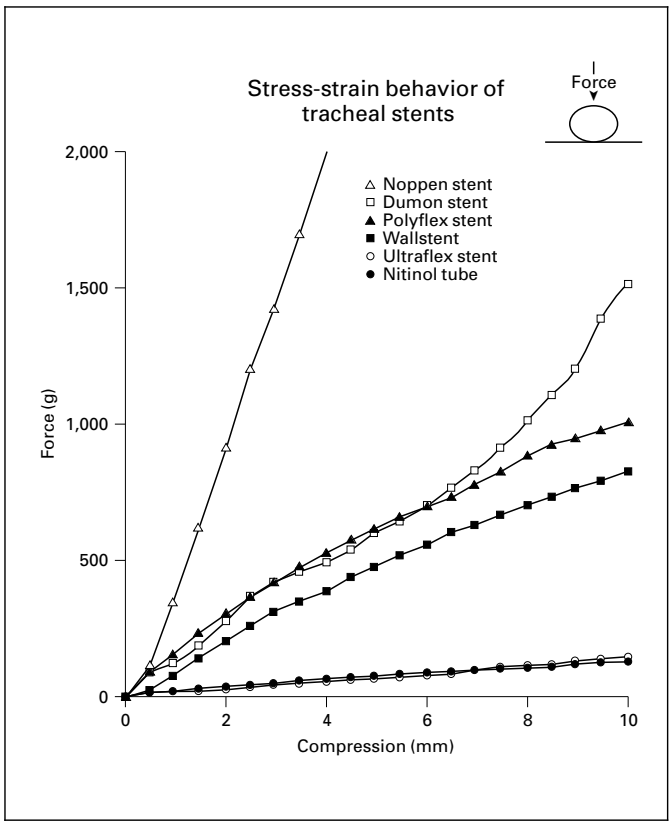

Fig. 9. Stress-strain curves of currently available tracheal stents. Lateral load (in gram) simulating tumor compression is plotted versus the decrease of diameter (in mm).

The biomechanical requirements are further complicated by the fact that nearly all available stents are round shaped, executing a circular uniformly distributed hoop strength. Typically, neither tumor stenoses nor benign strictures result in round-shaped constringent forces. While already the normal airways have a locally differing and nonlinear stress-strain behavior (e.g. the cartilage part and the membranous part) a stenotic area is totally irregular. A circular-shaped, concentrically expanding stent can hardly cope with a triangular-shaped scar stenosis of the trachea. Thus, locally high mucosal pressures cannot be avoided, giving rise to future destruction of mucosa and cartilage. Consequently, the stent itself, which was intended to treat an airway stenosis can cause a secondary stenosis due to unfavorable distribution of its tensile force.

Fig. 10. Cut and unilaterally sealed Dynamic bifurcation stent for the treatment of a stump fistula. Silicone rings around the tracheal and the bronchial limb enhance the sealing effect and help to prevent aspiration.

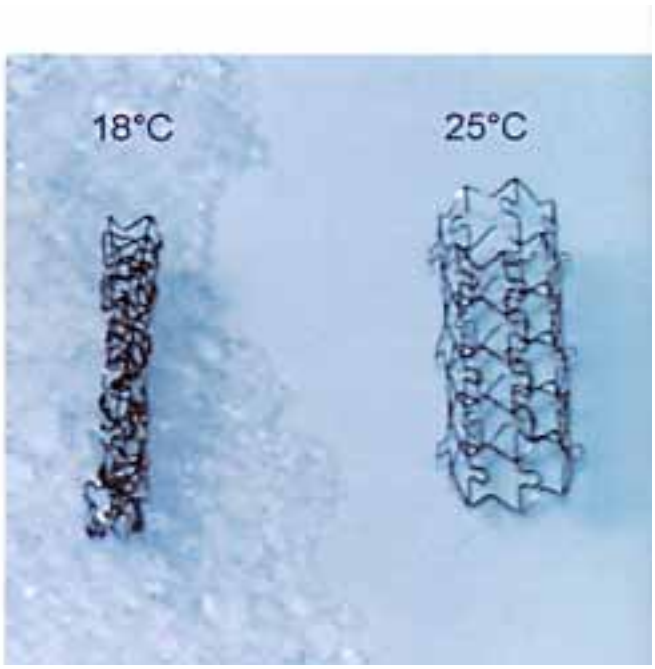

Fig. 11. A temperature-dependent nitinol stent can be squeezed down to less than 2 mm diameter if cooled below 20 °C. It opens up to 12 mm diameter at body temperature and applies sufficient force to counteract any tumor compression.

Special Stents, Customized Stents

While most anatomical problems can be managed with commercially available stents, there are conditions in which nothing off the shelf fits. Especially in patients after surgical procedures, the anatomy can be altered to such a degree that only a customized stent can solve the problem. Ignoring the warnings of the manufacturers and legal aspects we have occasionally combined silicone prostheses with simple silicone glue. The edges of the stents can be smoothed with a little electric grinding tool (Dremel). This works surprisingly well. We have not seen a single failure of these tailored stents. Figure 7 shows two cut and combined Dumon stents in a patient with tumor recurrence at the bifurcation site after left side pneumonectomy. Occasionally we have ordered angled and tapered Polyflex stents (Number 7 in fig. 5) for these indications. Wallstents have also been used for tumor treatment and for sealing fistulas after pneumonectomy [50]. If the problem of aspiration cannot be resolved satisfactorily, special stents can be fabricated. Figure 10 shows a cut and sealed Dynamic stent used in a patient with a huge stump fistula after pneumonectomy. Rings of silicone glue (Wacker Chemie, Munich, Germany) around the tracheal and the bronchial limb act as sealing rings. There was no further aspiration following the implantation of this customized stent.

It is possible to construct three-dimensional images of airway stenoses from CT or NMR scans [71]. In the foreseeable future, it should be possible to order customized stents for critical situations. Especially for patients with benign diseases and long lifetime expectations, these stents would be desirable. Rapid prototype techniques are available for orthopedic prostheses [72], and the only reason why these techniques have not been applied to tracheobronchial problems are financial matters.

Future Stents

The latest developments which we are currently testing include temperature-dependent nitinol stents that change their elastic properties if they warm up from room temperature to body temperature. A prototype of such a stent is shown in figure 11. This stent does not change its length under compression and adapts easily to curved stenoses. With newer models, the stent recoil can even be adjusted in vivo by applying heat with a saline-filled balloon catheter [56, 73, 74]. This fourth generation stent can be sof-

tened, e.g. if a patient responds to radiation therapy, or it can be made stronger in cases of tumor progression.

Another unique mechanical property of nitinol is the so-called stress-induced martensinitic transformation [42, 52, 53]. Prostheses taking advantage of this metallurgical phenomenon could be truly self-adapting. Such a stent would at least theoretically avoid pressure-related harm to the mucosa.

Researchers all over the world try to improve the biocompatibility of stents. Surface treatment with different coverings [13] or improved mechanical features [75] will lower the complication rates. Like coronary stents [76], airway stents could be loaded with radioactive material such as ^{32}P. This could prevent the development of granulation tissue formation. Another approach is the development of temporary stents that are completely bioabsorbable [77]. Stents made from self-reinforced Poly-*L*-lactides have revealed good biocompatibilty in animal experiments.

Airway stents are true enrichments, but after more than 10 years of frequent use, we are still in a kind of experimental stage. A lot of work is ahead to improve the iatrogenic foreign bodies. The industry partners tend to neglect the relatively small market of airway stents, and we physicians must use all our influence on them to improve their endoprostheses. Eventually, with combined efforts, the synergy of different techniques will result in better stents.

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Multimodality Treatment of Advanced Pulmonary Malignancies

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Summary

At the time of diagnosis, only 20–25% of lung cancers can be cured, primarily by surgery. Thus, for the large majority of patients presenting with inoperable, locally advanced or metastatic disease, treatment remains palliative. Classically, this treatment consists of external beam irradiation, chemotherapy or a combination of both. About 30% of all lung cancers present with neoplastic bronchial obstruction, and about 35% of all lung cancer patients will die from local intrathoracic complications, such as hemoptysis, respiratory infections and asphyxia. Local tumor control should therefore not only lead to palliation of the symptoms, but also to improved survival. With the rapidly developing field of interventional bronchoscopy with both the rigid as well as the flexible bronchoscope, a large variety of different endoscopic treatment modalities are now available which have shown their utility in controlling local tumor progression. The modern approach to inoperable pulmonary malignancies should therefore always include an endoscopic assessment of the central airways, and the term multimodality treatment should include endoscopic modalities. In patients exhibiting locally advanced tumors with central airway obstruction leading to moderate to severe symptoms and/or to an obstruction of >50% of the normal airway diameter, the initial combination of endoscopic with nonendoscopic therapy is recommended. Using endoscopic measures first leads to rapid relief of endobronchial obstruction, and subsequent radio- or chemotherapy helps to consolidate the initial therapeutic result. An exception to this rule can be made in untreated small cell carcinoma and lymphoma which can show dramatic response to chemotherapy. An algorithm for the management of locally advanced pulmonary malignancies is presented. Currently there are no data showing unequivocally what endoscopic treatment to use and what multimodality approach might be best in a certain situation. Therefore, prospective outcome studies are clearly needed.

The term multimodality treatment is frequently used in the oncological literature pertaining to the management of lung cancer. Only 20–25% of all lung cancers are curable at the time of diagnosis [1], and untreated, more than 95% of patients die within the first year [2]. In small cell lung cancer (SCLC) cure is possible in only 10–15%, and in non-small cell lung cancer (NSCLC), it is usually limited to the early stages (I–II, sometimes IIIA), and the treatment of choice is surgical resection. Current knowledge favors neoadjuvant therapy in stage IIIA followed by curative resection. For patients with locally advanced (stage IIIB) or metastatic disease (stage IV), cure is the

exception and treatment therefore mainly palliative. The options are chemotherapy, external beam irradiation or a combination of both. Combining various of these treatment options is called multimodality treatment. Interestingly enough, the addition of endoscopic treatment modalities to any of the above-mentioned therapies or to combinations of them is hardly ever mentioned in the oncological literature. On the other hand, the various endoscopic treatments are mainly discussed in the endoscopic literature without putting them into perspective with the nonendoscopic treatments. The main reason why this is so, is that therapeutic endoscopy is a fairly new area, and the majority of reports on evolving endoscopic treatments have been mainly descriptive, without proper outcome research data. The various emerging techniques have been described in many chapters of this book, and sometimes the term multimodality treatment is also used for a combination of purely endoscopic techniques. Today, endoscopic therapy has become an accepted modality in the therapeutic armamentarium against pulmonary malignancies, and therefore, the modern use of the term multimodality treatment of these tumors should encompass standard nonendoscopic and endoscopic treatment combinations.

It is the aim of this chapter to describe the rationale behind this inclusion of therapeutic endoscopy in the oncological approach, to suggest certain treatment combinations and finally to present an algorithm for the treatment of locally advanced lung cancer, which has been used successfully at our institution for many years. Two case descriptions with pictorial illustrations of standard situations of locally advanced pulmonary malignancies are added. They show the reader how multi-modality treatment is used to obtain the best possible palliation.

Standard Treatment for Lung Cancer

The grim prognostic situation of lung cancer patients is partly due to the late occurrence of symptoms which bring the patient to the doctor. In other words, the best prognosis is often encountered when lung cancer is diagnosed fortuitously in an asymptomatic patient (stage I and II). In rare cases, a very small peripheral tumor can lead to hemoptysis as an early symptom of a still curable tumor. The majority of patients will present with symptomatic disease, which is true for both NSCLC and SCLC. In NSCLC this often implies stage III–IV tumors. Stage IIIA tumors will still be considered operable for selected patients, who currently undergo neoadjuvant chemotherapy, resection and in some institutions adjuvant external beam irradiation [3]; stages IIIB and IV are inoperable. In SCLC, which is divided into limited and extensive disease, the treatment generally consists of chemotherapy and consolidating radiotherapy [4, 5], and although started with curative intent remains largely palliative. Only rarely are small peripheral SCLC lesions amenable to surgery, provided that a careful search for metastases is negative [6].

To this day, the majority of all patients (NSCLC, SCLC and pulmonary metastases) will therefore only receive some form of palliative treatment. Many different therapeutic modalities have evolved during the last 10–15 years. The following discussion will largely center on the treatment of NSCLC.

Treatment Modalities for Inoperable Lung Cancer

Currently, the treatment of symptomatic inoperable disease consists of some form of a combination of external beam irradiation and chemotherapy [7], which in the context of this chapter we call radio-/chemotherapy or nonendoscopic treatment. Chemotherapeutic regimens should contain cisplatin, if a maximal therapeutic effect is desired with acceptance of a higher toxicity. Various drug combinations have been tried successfully, such as cisplatin with vinorelbine [8]. Newer substances which have shown promise are paclitaxel [9], gemcitabine [10] and topotecan [11]. Nonendoscopic treatment combinations are usually the sole approach in the absence of stenosis of the central airways. Modern staging of lung cancer always includes bronchoscopy, and therefore the state of the central airways is known. About 30% of all lung cancers present with neoplastic bronchial obstruction, and about 35% of all lung cancer patients will die from local intrathoracic complications, such as hemoptysis, respiratory infections and asphyxia [12]. Local tumor control should therefore not only lead to palliation of symptoms, but also to increased survival. There are a large number of reports in the literature showing good palliation with either nonendoscopic or endoscopic treatment modalities. Some studies have also shown that relief of central airway obstruction can improve survival [13–15].

Multimodality treatment can be a combination of different endoscopic techniques or a combination of endoscopic with nonendoscopic treatments. Both combinations will be discussed in the following paragraphs.

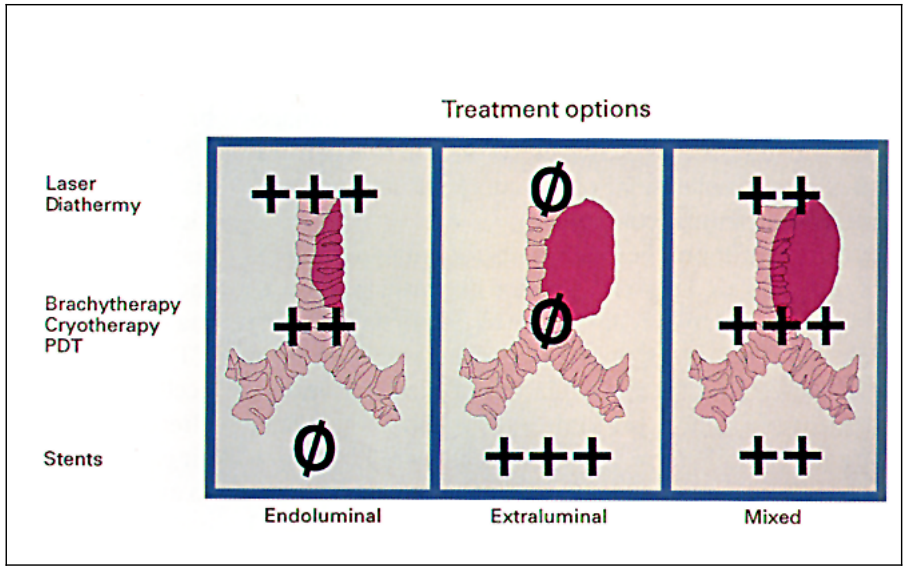

Fig. 1. Schematic illustration of the 3 main types of malignant central airway obstruction shown at the tracheal level with identical degrees of obstruction. Superimposed on the schema is the value of the various endoscopic modalities in treating these obstructions. +++ = excellent; ++ = good; ø = of no value.

Endobronchial Treatment Combinations

The various single treatment options are extensively discussed in the corresponding chapters in this book and will only be compared here. Figure 1 illustrates that some of these methods are largely competitive. Another comparison of the different endoscopic treatments is given in the chapter on cryotherapy by Vergnon and Mathur (table 3, page 142). For endobronchial or intrinsic obstructions, the most widely used technique is the Nd:YAG laser [16–18]. This laser is also excellent in the treatment of hemoptysis and can occasionally be curative in carcinoma in situ. One therapeutic session is enough to relieve even total obstruction of an airway. Similar results can be obtained with electrocautery or diathermy [19]. Both these methods can be used for elective as well as for emergent procedures, hence their popularity. As they are competitive, only one of the two is usually used in any given institution, and therefore, randomized studies comparing the two methods would be difficult to design and have so far not been conducted. There is, however, a clear difference in the cost of the equipment, electrocautery being at the most half the price of laser equipment. It has to be emphasized that in experienced hands working with the rigid bronchoscope for the relief of endoluminal obstructions, both the laser and electrocautery are mainly used for hemostasis. The actual debulking of the tumor is done by mechanical removal with a large forceps or, if possible, by shearing the tumor off the airway wall by rotating forward movements of the tip of the bronchoscope.

Whenever an airway lesion does not need immediate restoration of the airway lumen, techniques with a delayed effect can be used. This is the case when an airway is not threatened by rapid occlusion, or when a totally occluded airway is not vital for immediate survival. Techniques with delayed onset of action are cryotherapy [20], brachytherapy [21], which can complement laser resection [22], and photodynamic therapy [23]. All 3 techniques are largely competitive, and again no randomized trials exist which would compare them directly. The most widely used endoscopic treatment combination for endoluminal and mixed stenoses is laser resection followed by brachytherapy, which prolongs the time from initial reopening of an airway to the reappearance of local tumor growth.

If an airway is obstructed through extraluminal or extrinsic compression, simple dilatation is the best immediate procedure. This is achieved by the rigid bronchoscope, choosing increasing diameters of tubes, or by balloon dilatation, which is often gentler than the metal tip of the scope. Quite often, the effect of a mechanical dilatation, especially in malignant disorders, is very short-lived, in the order of 1–2 days. Sometimes the additional irritation during the dilatation causes additional swelling of the mucosa, leading to a worse situation than before dilatation. Therefore, the best and only treatment option for extrinsic airway compression is the placement of a stent or endobronchial prosthesis. A detailed description of the most important devices and their mechanical properties is given in the chapter by Freitag. Thus, stents are not

competitive to any other endoscopic treatment modality, they rather represent an ideal complement to other endoscopic techniques. This is especially true for the management of mixed stenoses, which are a combination of intraluminal and extraluminal obstructions, usually with an important intramural component.

In our institution, the best results for long-term patency of occluded airways with a mixed extrinsic and intrinsic component have been obtained by first removing endoluminal tumor by mechanical debulking with rigid bronchoscopy and laser coagulation of bleeding vessels, placement of a stent in the same setting, and 2 weeks later additional radiotherapy, either external beam irradiation or brachytherapy (usually 5–7.5 Gy at 1 cm from the center of the source – iridium-192 high-dose rate – applied 3 times in weekly intervals) [24]. Applying radiotherapy doubled the time to reoccurence of local tumor growth. Additional brachytherapy is very useful in patients who have already undergone full-dose external beam irradiation of 50–60 Gys, as brachytherapy can still be used safely. For patients without previous conventional radio-/chemotherapy, the options to be followed are outlined below.

Combinations of Endoscopic Treatment Modalities with Nonendoscopic Anticancer Treatments

Conventional management of inoperable lung cancer patients consists of radio-chemotherapy for symptomatic patients and a 'watch and wait' approach for asymptomatic patients. If the cancer is only locally advanced (usually stage IIIb), external beam irradiation to the primary tumor site and the mediastinum is the preferred treatment with a total dose of ~ 60 Gy. Some centers use higher doses, up to 70–80 Gy, in a clearly curative attempt, albeit at the price of clearly higher local toxicity. At our institution, a combined 'low-dose cisplatin' regimen with concurrent radiotherapy is used for stage IIIb NSCLC [7]. In metastatic disease, the preferred treatment is chemotherapy, or combined chemo-/radiotherapy [7]. The chemotherapy regimens vary constantly, but so far, the best results have been achieved with combinations containing cisplatin.

If a patient is asymptomatic with stage IIIb disease, treatment is sometimes withheld on the grounds that survival and quality of life are not influenced by a later inception of palliative therapy. On the other hand, it has been shown that a delay of initiation of chemotherapy until symptoms occur, is associated with a decreased therapeutic index. Further, a wait and see approach does not take the endobronchial situation into account. Whether bronchi are open or not is only indirectly assessed with the TNM classification by the presence or absence of atelectasis. This is a very crude way of analyzing airway involvement if one keeps in mind that obstructions of major airways usually do not lead to symptoms until at least 50% of the normal diameter is reduced. Further, lung parenchyma may contain a normal amount of air on chest X-ray or CT scan, even if the contributing airway is almost totally occluded, and normal ventilation and thus function are already abolished. In this situation, the small amount of air entering the lung mainly on deep inspiration is enough to avoid resorption atelectasis. This can be assessed clinically by the pathognomonic sign of late inspiratory localized wheezing or even better by spirometry with a loss of dynamic lung volumes such as the FEV_1 or the FVC. In an asymptomatic patient with a $>50\%$ obstruction of a main bronchus a watch and wait approach often leads to the patient coming back quite dyspneic, and the chest X-ray revealing atelectasis of an entire lung. One could argue that radio- or chemotherapy will then still be successful. Unfortunately, a good percentage of these patients present with additional postobstructive pneumonia, which is at least a relative contraindication for both external beam irradiation and chemotherapy. Therefore, the endoscopic situation should always be included in the decision making process of when to start what treatment. This will occasionally lead to endoscopic treatment of an asymptomatic patient with impending obstruction of a major airway. The type of endoscopic treatment chosen depends on the type of lesion, the equipment available and the personal preference of the endoscopist.

A special situation is the patient presenting with simultaneous obstruction of the central airways and additional upper vena cava syndrome. Efficient palliation can be achieved by a combination of endobronchial therapy and stenting of the vena cava. In life-threatening situations, the more urgent part is dealt with first. In our experience, initial stenting of the vena cava, sometimes including the subclavian veins leads to dramatic relief of venous obstruction within a few hours. Subsequent deblocking of the airways can then take place in a patient without cardiovascular compromise [25]. The first case history illustrates a multimodality treatment approach, combining vascular and bronchial stenting with external beam irradiation.

Case 1, a 65-year-old woman, had been diagnosed with locally advanced central (mediastinal and supraclavicular lymph nodes) squamous cell carcinoma of the lung. Her symptoms were a grade IV

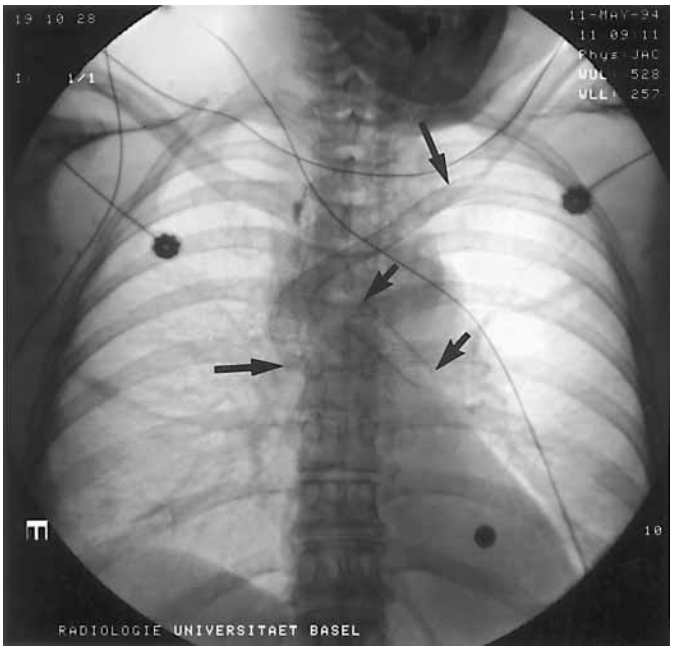

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Fig. 2. Chest roentgenogram of a 65-year-old woman with advanced central squamous cell carcinoma of the lung. Several uncovered Wallstents in the upper vena cava reaching into the left subclavian vein (long arrows) have been inserted to relieve severe symptoms from an upper vena cava syndrome. Also visible is a covered (covering not radiopaque) Airway Wallstent in the left main bronchus (short arrows) which was inserted because of an important extraluminal compression of the left main bronchus.

Fig. 3. Endoscopic view of the covered Airway Wallstent in the left main bronchus, seen radiographically in figure 2.

dyspnea, a left-sided pneumonia, and severe swelling of the neck and the head. They were caused by a subtotal obstruction of the left main bronchus and an upper vena cava syndrome. On an emergency basis several vascular stents were inserted into the left subclavian vein, the left brachiocephalic vein, as well as into the upper vena cava (uncovered Wallstents; fig. 2). This resulted in rapid resolution of the venous congestion, which also led to a slight decrease in dyspnea. Then, rigid bronchoscopy was performed. The left main bronchus was subtotally occluded partly by endoluminal tumor, partly by extraluminal compression. The endoluminal part was removed by coring it out with the tip of the rigid bronchoscope, hemostasis being achieved with the Nd:YAG laser. After passage of the rigid bronchoscope beyond the obstruction, massive pus drained from the left lung. The residual stenosis after dilatation with the rigid bronchoscope was >50% of the normal diameter, and the distal run-off showed normal left upper and lower lobe anatomy. Therefore, a covered Wallstent (Airway Wallstent) was inserted into the left main bronchus (fig. 3). The patient's dyspnea decreased from a grade IV to II, and most importantly, the Karnofsky scale increased from 20 to 50. She was discharged home and underwent subsequent external beam irradiation of 40 Gy to the tumor area and the mediastinum. Ten months after the initial diagnosis, the patient died of general cachexia. Her quality of life was acceptable for about 8 months, whereas without vascular and bronchial stenting, she would have died within a few days since her initial general condition with severe postobstructive pneumonia would not have allowed radio- or chemotherapy.

Another important point is when to opt for what treatment, or should endoscopic treatment precede or follow irradiation or chemotherapy. There are no data proving any approach of multimodality treatment superior to any other. At our institution, we have therefore empirically developed an algorithm for the treatment of patients with locally advanced lung cancer which incorporates both the classical tumor stage and the endoscopic situation of the central airways. These are usually defined as reaching from the trachea to the lobar orifices, sometimes down to the segmental level. The following section describes this algorithm and the rationale behind it.

Algorithm for the Combination of Different Treatment Modalities

In order to decide on the treatment options, it is primarily the clinical situation which will guide the clinician. In a stable situation, with the patient in a good general state and no obstruction of a central airway, treatment with radio- or chemotherapy will most often be sufficient.

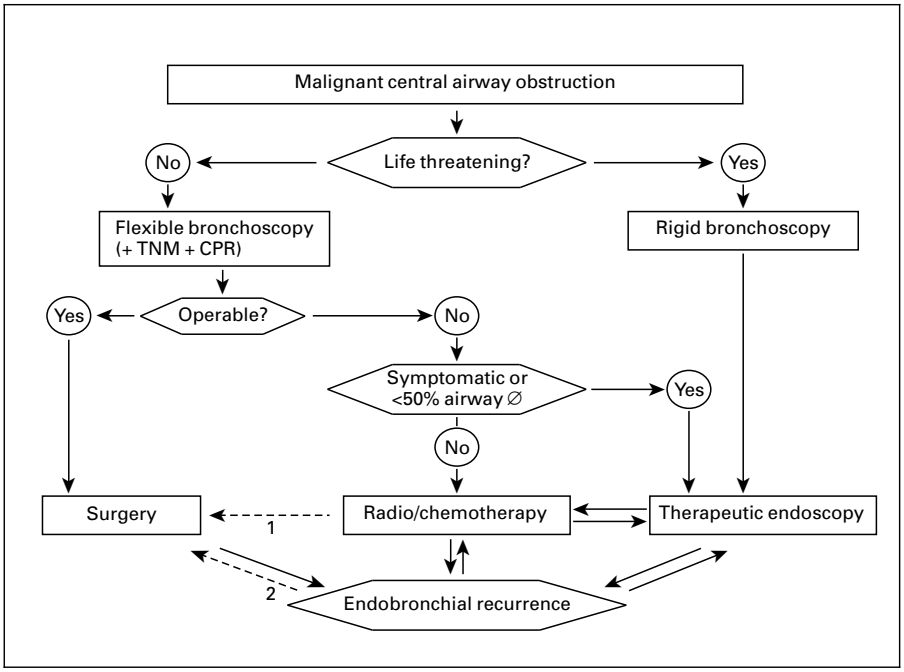


Fig. 4. Algorithm for the management of malignant central airway obstructions. Terms in hexogonal boxes are conditions, terms in rectangular boxes are procedures. Arrows in two directions indicate the tendency of endobronchial tumors to recur and the repetitive need of multimodality treatment. TNM = Tumor staging, including histology; CPR = cardiopulmonary reserves of the patient; interrupted arrows: 1 = rare cases of primarily inoperable lung cancers which become secondarily operable after initial therapeutic bronchoscopy usually followed by neoadjuvant treatment; 2 = rare cases of operated lung cancers initially presenting with central airway obstruction and still being operable after careful restaging of an endobronchial recurrence.

Endobronchial treatment is basically indicated in 3 situations: (1) life-threatening obstruction of the central airways (trachea, carina, main bronchi); (2) obstruction of the central airways causing symptoms (dyspnea, atelectasis, postobstructive pneumonia, hemoptysis) or reducing the airway lumen >50%, and (3) inoperable early lung cancer amenable to endoscopic treatment (multifocal synchronous lung cancers, insufficient cardiopulmonary reserves). The third indication is rare and is beyond the scope of this article. It represents, however, the most gratifying and therefore most interesting aspect of endobronchial therapy in malignant disease as endoscopic treatment modalities, such as brachytherapy, photodynamic therapy, laser, cryotherapy and electrocautery can all be tried with curative intent in these situations [26, 27]. The topic is dealt with in the corresponding chapters of this book.

In practice, patients with central airway obstruction present with indicative symptoms and signs. They usually are dyspnea, hemoptysis, atelectasis, cough and fever in the case of postobstructive pneumonia. Less frequently, thoracic pain is the leading symptom. The management of such patients depends on the etiology of the obstruction, its location and its degree. In benign lesions – which are not addressed further in this chapter – surgery should always be contemplated and its risks and benefits weighed against endobronchial procedures. The large majority of bronchologic patients present with malignant lesions which are generally not amenable to surgery, and the goal of treatment is palliation.

It is mainly for these situations that we have developed the algorithm depicted in figure 4. If clinical assessment including radiological examinations (plain film and/or CT scan of the thorax) and initial bronchoscopy reveal central airway stenosis in an inoperable patient, we advocate a combination of endoscopic and nonendoscopic cancer therapy. In principle, we prefer to use endoscopic measures first, followed by nonendoscopic therapy, whenever the involved airway causes serious symptoms and/or the degree of obstruction is >50% of the normal airway diameter. This pathway has clear advantages. In life-threatening situations, in the case of tracheal obstructions, it is mandatory for the immediate survival of the patient. In less urgent conditions which do not warrant immediate attention, such as moderately severe tracheal obstructions or total obstructions situated further distal in a main or lobar bronchus, some people might start with nonendoscopic treatment if this option has not been used previously. We prefer to start with endoscopic measures in this situation also. Often, the patient will suffer from some degree of postobstructive retention of secretions or even pneumonia. This is at least a relative contraindication for external beam irradiation or chemotherapy. Further, if external beam irradiation is applied first, the bron-

chi reopen, but if the endobronchial involvement has been important – long stenoses, destruction of airway walls – the radiation effect often causes postactinic scarring, resulting in distortion of the airway anatomy with impaired mucus clearance [24, 28]. On the other hand, an airway obstruction of $<50\%$ of the normal diameter often does not cause symptoms and usually disappears completely after conventional radio-/chemotherapy. In these situations, we refrain from starting with endoscopic treatment. On the other hand, if the fiberoptic diagnostic examination reveals a 'technically appealing' lesion, generally a short endoluminal tumor, which is judged to be treatable under local anesthesia, we immediately proceed with therapeutic bronchoscopy, provided that the estimated procedure time does not exceed 30 min.

An exception to this general approach is sometimes possible in patients presenting with untreated SCLC or lymphoma. Even severe airway obstructions, clearly exceeding 50% of the normal diameter, can react dramatically to initial chemotherapy within 1–2 days. In these situations, we start with chemotherapy first, unless the situation is immediately life-threatening.

The type of the initial endoscopic treatment will depend on the nature and the extent of the obstruction, as well as on the equipment available (fig. 1). An endoluminal tumor should be removed by laser, electrocoagulation and mechanical coring out if immediate reopening of the airway is the goal. Cryotherapy or photodynamic therapy can be used for nonvital situations, as their therapeutic effect is delayed for about 2–3 weeks. Another endoscopic modality with delayed effect only is brachytherapy, which has the advantage of effectively treating lesions at a distance of up to 1 cm of the center of the source, most often reaching beyond the airway wall. It is therefore an ideal complement for the treatment of intramural components of airway obstructions.

Extrinsic stenoses are dilated with the rigid bronchoscope or with a balloon used with either the rigid or flexible bronchoscope, and continued patency is guaranteed by insertion of a stent. In mixed stenoses, the endoluminal tumor is first removed, and if the remaining extrinsic and/or intramural component after resection and dilatation is $>50\%$ of the normal lumen, a stent is also inserted. We also favor stent insertion if a patient has a posttreatment lumen patency of $>50\%$, but shows unstable airway walls due to destruction of the supporting cartilaginous structures. Further, we insert stents in patients who have no further treatment options, irrespective of the airway diameter at the end of the endobronchial procedure. This usually means the patients have had full-dose external beam irradiation, exhausted chemotherapy and have undergone full treatment of 15–20 Gy brachytherapy.

If nonendoscopic treatment is still available, external beam irradiation and/or chemotherapy should be initiated within 2 weeks after the endobronchial treatment to consolidate the local effect. A full radiation dose of up to 50 Gy is usually applied to the mediastinum, including the endoscopically pretreated stenotic segment. The chemotherapy regimen will depend on tumor histology and local preferences. Patients who have had full-dose external beam irradiation should undergo brachytherapy. In our institution they undergo 3 sessions with a HDR-iridium-192 afterloading source which will lead to a total dose of ~ 15 Gy at a distance of 1 cm from the source. In our experience, it takes only about 2–3 months, depending on tumor biology and the site of the initial stenosis, until local tumor recurrence leads to reobstruction of an airway which has been treated by laser resection only [24]. Insertion of a stent usually extends this period somewhat, but eventually the tumor will obstruct the airway proximally and distally to the stent. When we compared patients after stent insertion with and without subsequent radiotherapy, the group who underwent radiotherapy showed no reobstruction for at least 4–6 months in comparison to 2–3 months in the group without radiotherapy [24]. A classical approach used at our institution is illustrated by the second case history.

Case 2, a 54-year-old man, consulted his general practitioner because of increased cough, blood-tinged sputum and a weight loss of 7 kg over 3 months. He was a tiler, current smoker with a 40 pack-year history and consumed about 1.5 liters of beer a day. His chest roentgenogram showed an ill-defined hilar opacity at the level of the right upper lobe, which on chest CT scan was highly suspicious of a locally advanced upper lobe tumor with invasion of the mediastinum and partial obstruction of the right main bronchus (fig. 5). This was confirmed by bronchoscopy, showing a mixed subtotal obstruction of the right main bronchus (fig. 6) which could easily be passed with a closed forceps. Additionally, there was an inward bulging of the right tracheobronchial angle due to compression by the tumor. Histology obtained by a forceps biopsy during bronchoscopy revealed squamous cell carcinoma. The patient had a grade III dyspnea and corresponding severe restrictive airflow limitation with an FEV_1 of 1.3 liters (39%) and an FVC of 2.4 liters (57%). A search for metastases (bone and brain scans) remained negative, leading to a clinical diagnosis of a highly symptomatic locally advanced (stage IIIb) squamous cell carcinoma with impending atelectasis of the right lung. The patient therefore first underwent rigid bronchoscopy with dilatation of the right main bronchus, which revealed a practically occluded right upper lobe entrance but a normal intermediate bronchus with normal middle and lower lobes. A spiked polyflex stent was inserted into the right main bronchus (fig. 7), which resulted in immediate improvement of the patient's dyspnea to a grade II correlating with a marked improvement in FEV_1 to 2.0 liters (62%) and FVC to

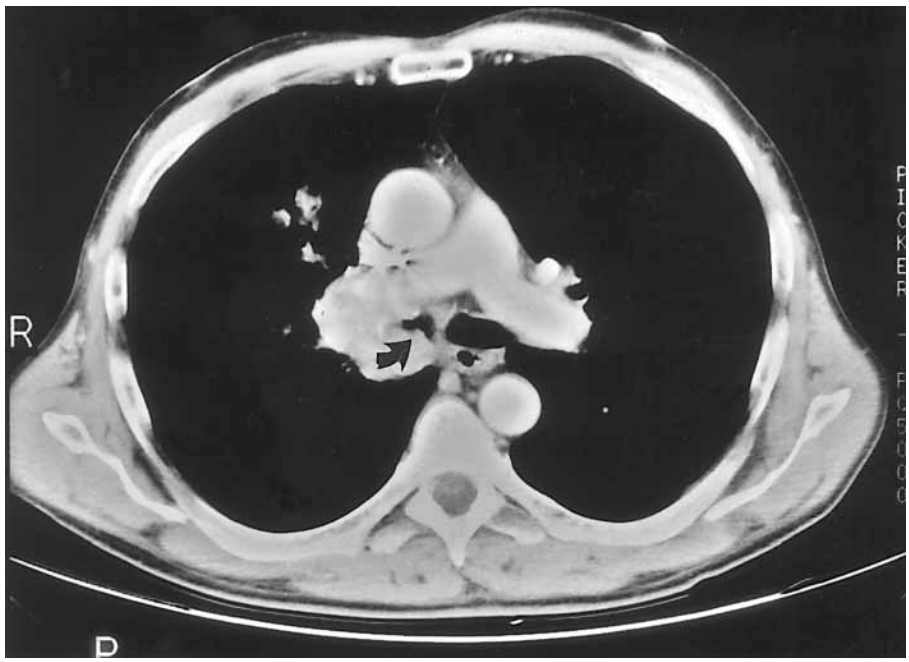


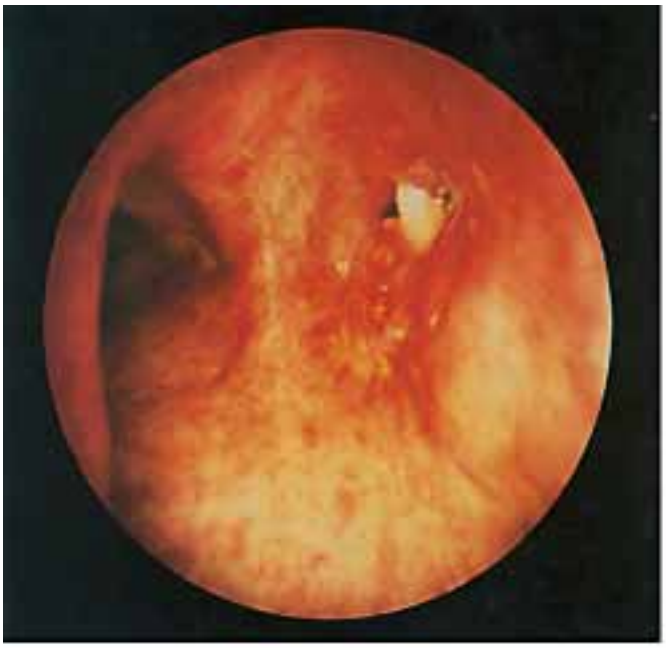
Fig. 5. CT scan at the level of the main carina of a 54-year-old male smoker with blood-tinged sputum. High suspicion of locally advanced right upper lobe tumor with invasion of the mediastinum and partial obstruction (curved arrow) of the right main bronchus.

2.9 liters (71%); further, retained secretions were expectorated, and the cough virtually disappeared. The patient then underwent external beam irradiation of the tumor and the mediastinum with a total dose of 39.6 Gy. Three months after stent placement, the patient did well, but a routine control bronchoscopy showed that the stent had partially migrated, its tip lying in the trachea. This migration was due to the radiation effect leading to shrinkage of the endobronchial tumor mass. The stent was removed during flexible bronchoscopy, showing a stent bed which was stable and only slightly reduced in diameter (fig. 8). Another 3 months later, a routine control bronchoscopy revealed squamous cell carcinoma in a mucosal biopsy of the right main bronchus; the patient still did well. To prevent recurrent endobronchial tumor growth, it was therefore decided to continue with brachytherapy (3 sessions at ~5 Gy at 1 cm from source at weekly intervals), which the patient is still undergoing at the time of writing. In summary, this patient profited immediately from interventional bronchoscopy with stent placement, patency of the right main bronchus helped save the function of middle and lower lobe and subsequent radiotherapy consolidated this initial effect.

Eventually endobronchial recurrence of previously treated central airway obstruction is the rule. Generally repetitive sessions of therapeutic endoscopy are necessary to guarantee sustained airway patency (fig. 4). In patients who have not exhausted conventional radio-/chemotherapy, this option should be tried. The result of carefully titrated multimodality treatment will increase the number of patients who will have patent central airways until their death.

So, what do these patients die of? A large proportion will succumb to metastatic disease, the ones dying of local intrathoracic complications often experience fatal thromboembolic incidents, suffer from intractable malignant pleural or pericardial effusions, develop upper vena cava syndrome, or in our experience very often develop terminal pneumonia in a state of general tumor cachexia. On the other hand, there is a higher proportion of fatal hemoptysis in patients having undergone interventional bronchoscopic treatment, especially after brachytherapy (see chapter on brachytherapy by Fischer and Huber). It is not clear to what extent this complication can be attributed to the treatment per se or simply to the fact that this treatment keeps the airways open, allowing fragile vessels to erode into them rather than into a compact tumor bed containing the hemorrhage.

The important message of the addition of endoscopic treatment modalities to the armamentarium of anticancer therapy of pulmonary malignancies is that the available data unequivocally show very efficient palliation of symptoms. What methods should be used for what situation and what multimodality approach is best remains to be elucidated, randomized trials are clearly needed. A first example in the right direction was set by Huber et al. [29], in a randomized study comparing external beam irradiation alone to the combination of external beam irradia-



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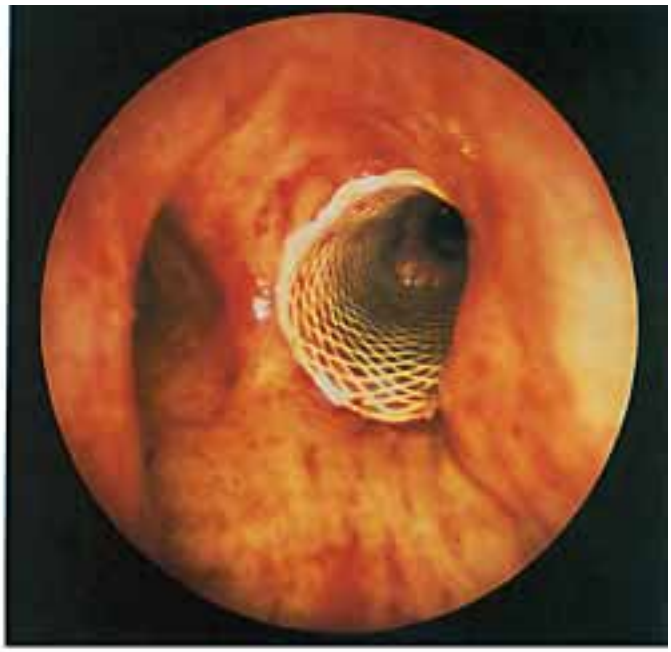

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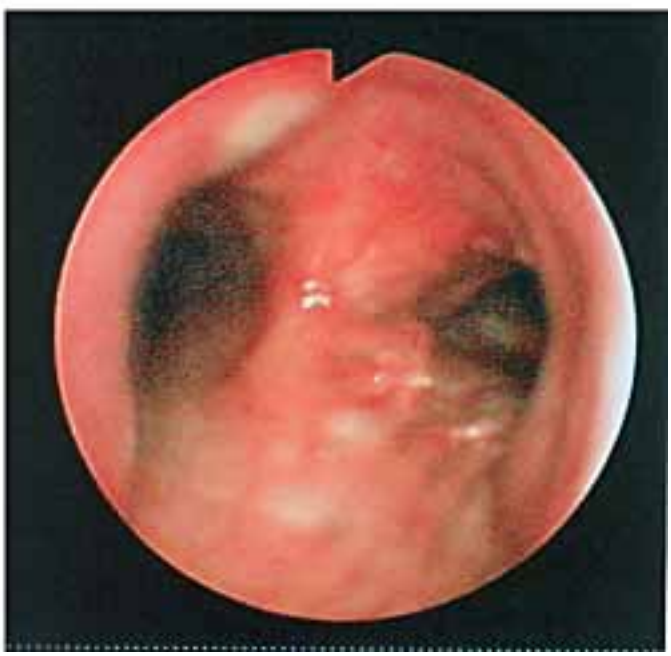

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Fig. 6. Endoscopic view of the patient of figure 5, confirming the locally advanced tumor with subtotal mixed obstruction of the right main bronchus and inward bulging of the right tracheobronchial angle.

Fig. 7. A polyflex stent (Rüsch AG, Waiblingen, Germany) has been inserted after laser resection of the endobronchial tumor and balloon dilatation of the extraluminal component of the stenosis of the right main bronchus.

Fig. 8. Aspect of right main bronchus 3 months after completion of external beam irradiation and removal of the partially migrated stent. The right main bronchus is patent with stable walls, the lumen is only moderately narrowed.

tion and brachytherapy in patients with locally advanced lung cancer. Additional brachytherapy resulted in significantly longer local tumor control, but not median survival. For a subgroup of patients with squamous cell carcinoma, however, survival after additional brachytherapy was longer (40 vs. 33 weeks); but this difference did not reach statistical significance ($p = 0.09$). The incidence of fatal hemoptysis was not different between the two groups.

In agreement with other authors [30–32], we suggest that in locally advanced pulmonary malignancies with involvement of the central airways (causing moderate to severe symptoms and/or a reduction of the involved air-

way lumen of >50% of the normal diameter), it is best to combine endoscopic and nonendoscopic treatment modalities from the start, which will prolong the time until recurrence of local tumor and may improve survival. At our institution, we generally prefer to start with endoscopic treatment, using techniques with immediate effect (laser, coring out, dilatation and stent placement). The patient will thus be able to experience rapid, sustained symptom relief, which allows him to enjoy life in a fairly preserved state of health.

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Percutaneous Imaging-Guided Interventional Procedures in the Thorax

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Summary

Imaging-guided nonvascular diagnostic and therapeutic procedures in the chest are applicable in the lung, pleura and mediastinum. Guidance systems include uni- or biplanar fluoroscopy, ultrasound, CT and MR or a combination of these. Percutaneous tissue sampling of a thoracic lesion is indicated when histological diagnosis will modify the stage of the disease or influence therapeutic strategy, and when the diagnosis is not obtained by endobronchial techniques. Cytology and histology obtained by small-gauge needle biopsy confirm malignancy in 80–95% of cases at low cost and carry a low incidence of major complications. Thoracic fluid or gazeous collections located in the pleural space, pericardium, lung and mediastinum can be aspirated or drained by a closed percutaneous catheter insertion with imaging guidance techniques using catheters of variable size and design. The potential of percutaneous therapy supersedes blind technique and surgery. Clinical success of catheter drainage of pleural empyema varies from 80 to 100%, when drainage is performed in a first attempt or after failure of other techniques. Minimally invasive drainage of lung abscesses and mediastinal abscesses show similar success rates, but patients referred often exhibit a bad prognosis. Further refinement is achieved by local instillation of fibrinolytic agents in selected cases of empyema and hemothorax. These procedures are cost effective and complementary to endobronchial procedures and surgery.

Percutaneous Transthoracic Needle Biopsy

Percutaneous lung biopsy was first described by Leyden in 1883 to establish the infectious nature of lung disease. Currently, percutaneous tissue sampling of a pulmonary, pleural or mediastinal lesion is indicated when histological diagnosis will further influence diagnostic strategy and therapeutical options, or modify tumor staging and the sequence of cancer treatment. Cost efficiency by shortening hospital stay was demonstrated [1].

Indications

Main indications for percutaneous transthoracic needle biopsy (PTNB) can be summarized as follows [2]: pulmonary nodule(s) without specific diagnostic criteria on computed tomography (CT) ascertaining benignity; pulmonary nodule(s) or mass suggestive of malignancy, when surgery will be postponed, or replaced by chemotherapy and/or radiotherapy – a patient who refuses invasive diagnostic procedures and therapy may change his mind, when irrefutable proof of malignancy is established by percutaneous biopsy – pulmonary nodule(s) in a patient with a history of extrapulmonary primary malignancy and in clinical remission or presenting several primary malignancies; a residual nonregressive lesion following radiotherapy or chemotherapy; tissue sampling for therapeutic sensitivity tests; measurements of tumor markers; hormone dependence; DNA analysis; chronic diffuse pulmo-

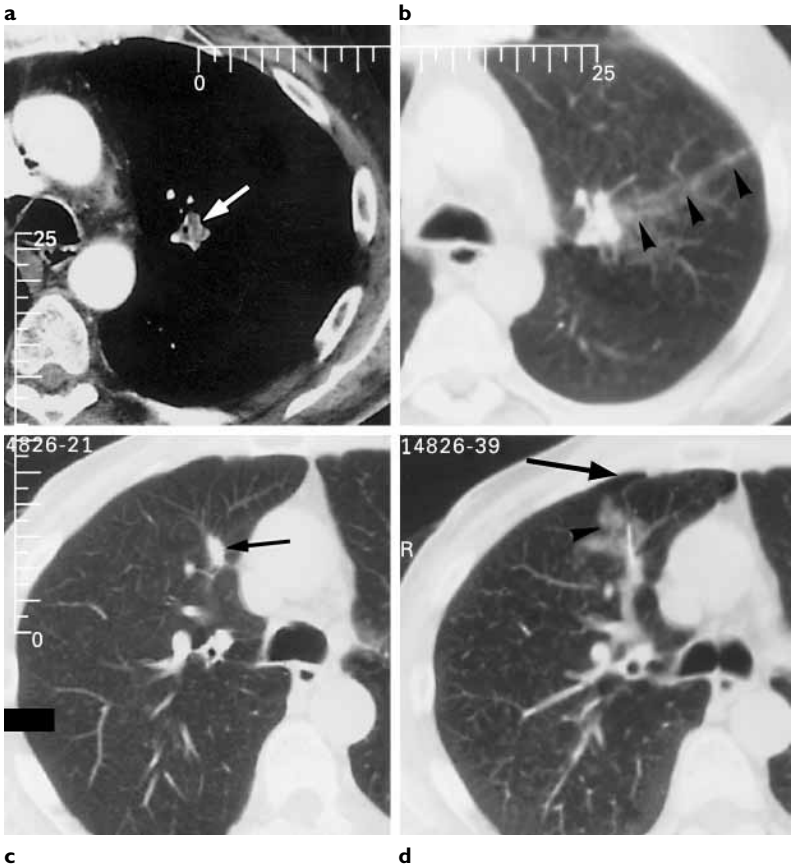

Fig. 1. PTNB of a small pulmonary nodule in 2 different patients. **a, b** An 11-mm nodule (arrow) is evidenced in the left upper lobe in a central location. Two previous fiberoptic bronchoscopies with transbronchial biopsies were negative. PTNB was performed with a 21-gauge needle, which revealed small cell lung cancer. Note the small alveolar blood flooding along the needle track (arrowheads). No complication occurred. **c, d** PTNB of a 9-mm solitary right pulmonary nodule (arrow) which showed large cell carcinoma on cytology and histology. Note a small anterior pneumothorax (long arrow) and limited perinodular hemorrhage (arrowhead).

nary infiltrate in selected cases; pleural nodule or mass of indeterminate origin; mediastinal mass or adenopathy. The need for preoperative diagnosis of a solitary pulmonary nodule varies between institutions and depends on the pretest probability of diagnosing a lesion that would obviate an unnecessary thoracoscopy or thoracotomy, and the demand of the patient [3]. Concerning X-ray and CT characteristics of pulmonary nodules, the following observations should be remembered: 43% of nodules with a diameter smaller than 1 cm are benign; 97% of nodules with a diameter larger than 3 cm are malignant; 33% of primary malignant nodules have regular contours; 46% of benign nodules are spiculated; 26% of benign nodules and 5% of malignant nodules show microcalcifications on CT; 21% of benign and 40% of malignant nodules contain an air-bronchogram. Overall, a correct diagnosis is established with CT in 66–98% of cases [4].

PTNB is a useful alternative to mediastinoscopy or mediastinotomy for tissue diagnosis of enlarged hilar or mediastinal lymph nodes. All areas of the mediastinum are accessible to PTNB. The technique is faster, better tolerated and less expensive [5].

Percutaneous puncture is also indicated in other conditions: intracavitary injection for treatment of secondary aspergillomas [6]; insertion of a harpoon or injection of methylene blue or black carbon as a localizer prior to pleuroscopic or video-assisted thoracic surgery (VATS) of lung nodules or highest yield areas for infiltrative disease [7–10] and percutaneous brachytherapy of pulmonary malignancy [11]. Lesions with a diameter of less than 3 cm, seated in the outer third of the lung or near a fissure are usually considered.

Contraindications

Vascular structures such as aneurysm or pulmonary arteriovenous malformation, hydatid cyst, meningocele and mediastinal pheochromocytoma are absolute contraindications of PTNB. The correct diagnosis should be established with cross section imaging, including angiography. The following are relative contraindications: puncture of both lungs during the same day, puncture of only one functional lung, chronic respiratory insufficiency, pulmonary arterial hypertension, cardiac insufficiency, recent myocardial infarct, angor, severe emphysema and

bullae situated in the vicinity of the pulmonary lesion. A coagulation defect should be recognized and corrected before sampling. Cough, dyspnea and reduced patient cooperation are other limiting factors. Mechanical ventilation is a relative contraindication of PTNB.

Technique

PTNB is preferentially performed with uni- or biplanar fluoroscopy control, when the target can be precisely localized [12, 13]. It should be remembered that projection of a lesion can vary over 4 cm when changing position from supine to prone. The needle path should avoid traversing intercostal vessels (i.e. needle entry is optimally defined at mid intercostal space). A lesion that is difficult to see with fluoroscopy can be localized with CT [14]. CT is particularly useful for lesions that are situated at the apex and the base of the lung, in the posterior sulcus or at the pulmonary hilum (fig. 1). Mediastinal and hilar vascular structures surrounding a lesion are recognized with contrast-enhanced CT. In complex situations, CT may reveal a tumor obscured by atelectasis, obstructive pneumonia or pleural effusion. Central tumor necrosis is recognized on the basis of central low densities after intravenous contrast injection. The biopsy needle should be directed to the viable tumor component situated at the periphery of the lesion. CT recognizes the pleural fissures and avoids lobar transgression. Nonaerated lung or symphyses established between a pulmonary lesion and the pleura allow use of this needle pathway and thus minimize the risk of pneumothorax. PTNB performed at the side of pneumonectomy to disclose local cancer recurrence is best monitored with CT. Spiral scanning was not proved superior to conventional CT in monitoring percutaneous lung biopsy in our experience, based upon a prospective comparative study [15]. It is more time consuming and should be applied only in those cases, when identification of the needle tip is problematic in a noncooperative patient or when an oblique pathway of the needle is necessary. Real-time CT (fluoro-CT or continuous CT) is now becoming widely available and makes CT control even more expeditive [16]. Slices or a lung volume can be acquired continuously and allows a reliable control of the procedure. Ultrasound (US) can be used as a guidance for puncture of pleural or subpleural lesions [17] (fig. 2). A large number of cutting or aspiration biopsy needles, including automatic pistols with a needle calibre of less than 1 mm and a variable tip design are currently used (fig. 3). Almost all needles allow cytological and histological samples and give similar rates of results and complications. Several percutaneous passes are performed when the anticipated risk of complications is low.

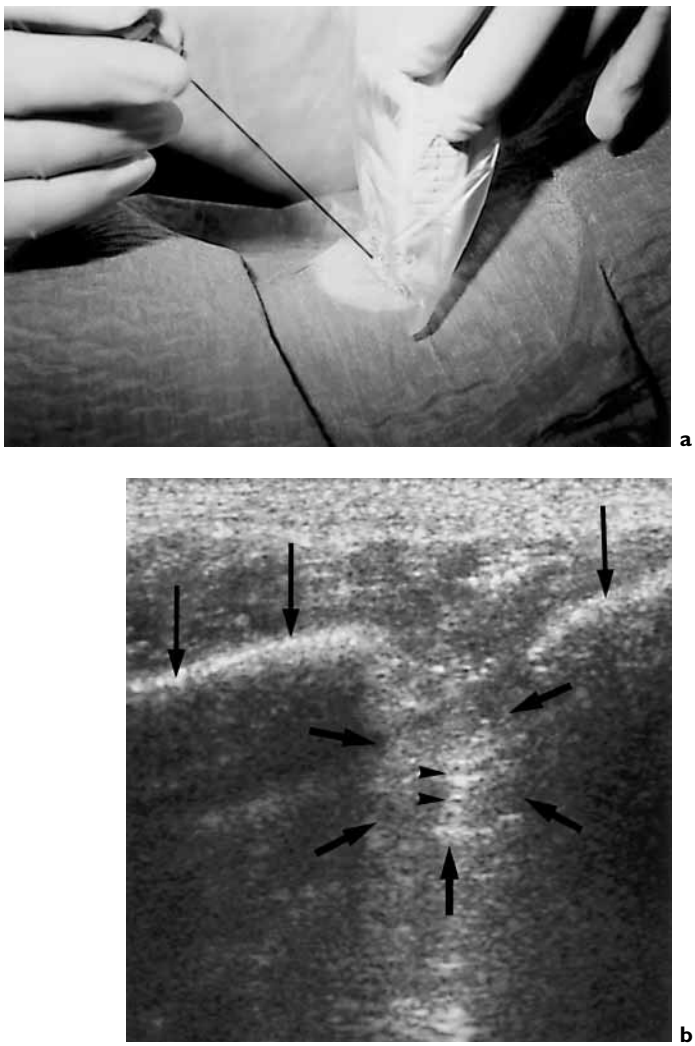

Fig. 2. Free-hand US-guided PTNB of a pulmonary nodule. **a** The operator controls the US probe by one hand and the biopsy needle by the other hand. Sterile gel is applied on the skin of the patient for optimal US transmission. **b** US view obtained through the intercostal space demonstrates an acoustic shadow behind the ribs (long arrows) and a subpleural mass (arrows) in close contact with the pleura. The vertical white dots (arrowheads) represent the artifact created by the needle inside the mass. Pathological results revealed poorly differentiated squamous cell carcinoma.

Results

PTNB has an accuracy varying from 80 to 95% in confirmation of malignancy [14, 18–26]. In a comparative study, sputum and bronchial aspiration alone were diag-

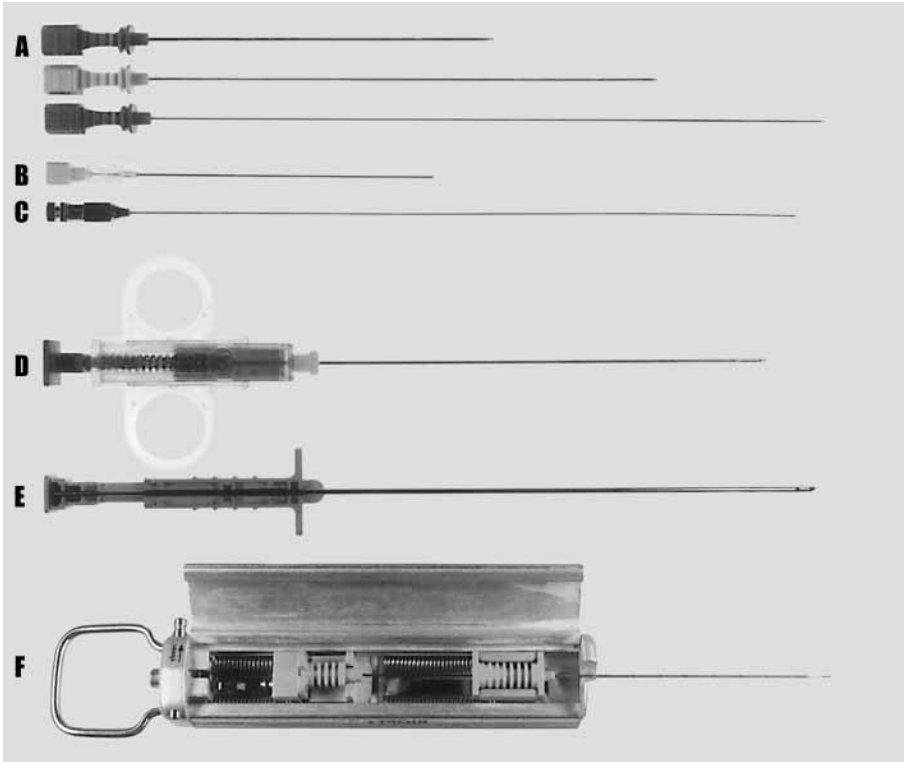

Fig. 3. Most frequently used needles to perform PTNB. Aspiration needles: Otto needles of different size and length (18 G, 10 cm; 19.5 G, 15 cm; 21 G, 20 cm; A), such needles allow for cytological smears and histological specimens; spinal needle (20 G, 10 cm; B); Chiba needle (22 G, 20 cm; C). Cutting needles: tru-cut (19 G, 15 cm; D); tru-cut (14 G, 15 cm; E); for parietal or mediastinal biopsy; biopsy gun with cutting needle (F); such a device can be difficult to handle without moving the tip of the needle in critical situations.

nostic of cancer in 5.4%, PTNB alone in 72.6% and both techniques were in agreement in 22% [25]. Inadequate cytologic smears may be noted in up to 17% and allowed no interpretation in 9% in larger series [27]. Additional false-negative diagnoses are obtained in about 5% and are caused by inadequate sampling, tumor necrosis, crushed cells or errors in sampling reading. Negative predictive value of percutaneous pulmonary biopsy is 84–96%, and false-positive results are noted in 2–4% [12, 27]. Diagnostic accuracy for small nodules (<15 mm) is similar to larger lesions [28] (fig. 1). The following criteria should be fulfilled to ascertain that a lung nodule is benign: a technically successful biopsy, adequate aspiration that is not normal lung, no suspicion of cancer on the aspirated cells and normal bronchoscopy. If a specific benign diagnosis can be reached, no further exploration is required. Most frequently, a nonspecific and nonmalignant inflammatory process is evidenced on the cytological smears. These lesions should be followed up for 2 years [22]. If the sampled material is inadequate or insufficient, or in case of cytologic or clinical suspicion of malignancy, the biopsy should be repeated. The literature reported a mean specific benign diagnosis in 25% of patients (table 1). Most mediastinal lesions are of metastatic or lymphomatous origin. Results of PTNB are similar to those of lung biopsy, when metastatic adenopathies are considered. Diagnosis of mediastinal non-Hodgkin lymphoma gives better results when comparison of smears or tissue fragments with a previous sampling or another extrathoracic site is available. Confirmation of Hodgkin's disease is difficult,

Table 1. Transthoracic needle biopsy of benign lung nodules

Authors	Benign lesions biopsied	Specific benign diagnosis
Flower and Verney [13]	75	18 (24)
Johnston [25]	–	– (11.7)
Horrigan et al. [23]	8	2 (25)
Khouri et al. [22]	137	93 (67.8)
Greene et al. [21]	27	12 (44)
Winning et al. [24]	43	7 (16)
Calhoun et al. [20]	132	16 (12)
Perlmutt et al. [29]	–	– (12)
Charig et al. [26]	–	– (5)

Figures in parentheses are percentages.

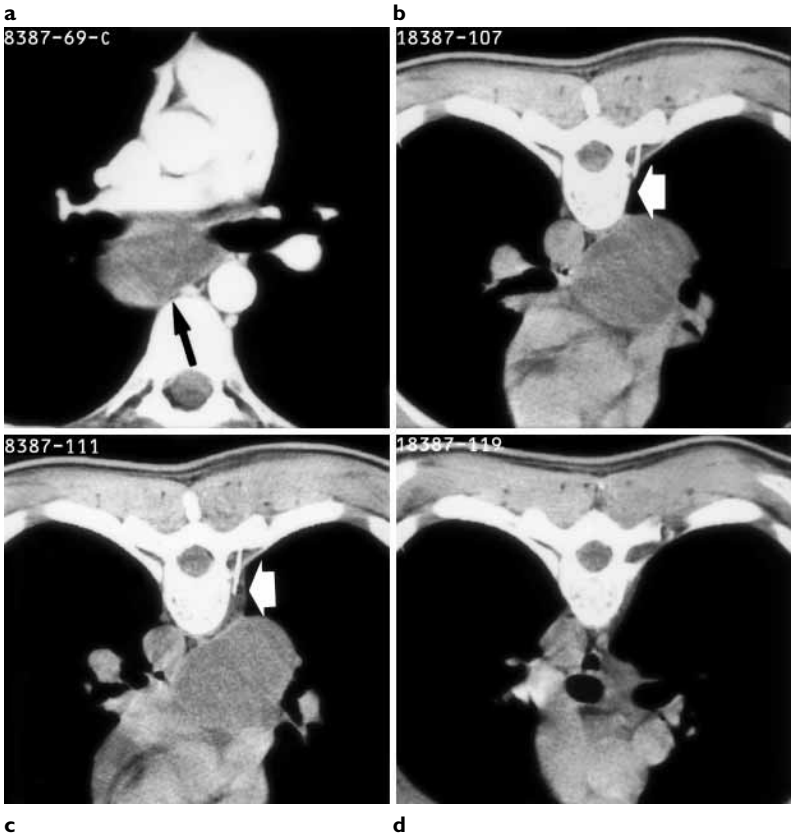

Fig. 4. Widening of the extrapleural space for safe PTNB of mediastinal lesion. **a** Contrast-enhanced CT demonstrates a subcarinal mass highly suggestive of a bronchogenic cyst (arrow). **b** CT-guided PTNB performed in the prone position. Absence of extrapleural fat planes prevents safe mediastinal access (large arrow). **c** Widening of the extrapleural space is obtained by injection of 20 ml of saline while advancing the tip of the needle towards the lesion (large arrow). **d** Complete aspiration confirmed the diagnosis of bronchogenic cyst.

particularly in the scleronodular type or following mediastinal radiotherapy. Inconclusive results are obtained in tumors of the thymus or other primary malignant neoplasms of the mediastinum, and in malignant pleural tumors, even when large cutting needles are used. Examination of the entire resected specimen often remains mandatory. Nevertheless, recent studies have demonstrated that cutting-needle biopsies provide diagnostic material in patients with lymphoma that is sufficient to guide therapy in 83–95% of patients as well as in diffuse pleural thickening [3].

Complications

Pneumothorax is the most frequent complication following PTNB, with an incidence of 8–60%. Less than 5% of patients have persistent clinical symptoms and require aspiration or drainage. Factors influencing pneumothorax are: age, collaboration, respiratory function, elasticity of lung parenchyma, biopsy technique, experience of the operator, duration of the procedure, number of needle passes, diameter and flexibility of the needle, emphysema, difficult localization of the target, depth and diameter of the target, mechanical ventilation and cavitary lesion. Special care should be taken in patients who underwent thoracic surgical intervention with a potential communication between both pleural spaces, increasing the risk of bilateral pneumothorax. Best prevention of complications is to perform the procedure rapidly and to reduce the number of passes by inspecting the quality of smears or fragments after each puncture. Pneumothorax is further prevented by the roll-over technique, which consists in turning the patient, following biopsy, for 15–30 min on the side which had been punctured. All patients are maintained in the recumbent position for 4 h after biopsy, then an erect chest radiograph is obtained. If no pneumothorax is present, compliant patients can be discharged. Asymptomatic patients with a pneumothorax covering one third or less of the lung field are also discharged if the pneumothorax remains stable for 3–4 h. The patient and the accompanying persons are advised to return to the hospital when symptoms suggestive of complications (cough, chest pain, shortness of breath) are noticed. When a large or symptomatic pneumothorax persists, a Heimlich valve is inserted under fluoroscopy control. A 7F to 10F catheter with multiple sideholes is inserted in the pleural cavity using the trocar or the angiographic catheter exchange

Table 2. Comparison of different diagnostic modalities of pulmonary lesions

Technique	Availability	Total cost including hospital stay	Diagnostic accuracy %	Pneumothorax %	Diagnosis and treatment
Bronchoscopy	+++	1 N	30–90	1–3	(+)
PTNB	+++	1–2 N	80–95	8–60	–
Thoracoscopy	++	20–30 N	≥95	100	yes
Thoracotomy	+++	40–80 N	~ 100%	100	yes

N = Mean cost of bronchoscopy.

technique. The pneumothorax is aspirated with a syringe, the valve is connected, and its function is checked before the patient is discharged. The catheter is sutured to the skin and the Heimlich valve is loosely attached to the waist. Some patients may be sent home and recalled the next day for a control chest X-ray. In our experience, the pneumothorax had disappeared in all cases. If the pneumothorax occurs during mediastinal biopsy, biopsy is completed before the pneumothorax is treated. In the literature, small bore catheter drainage of iatrogenic pneumothorax is successful in 75–97% [30–32]. Complications include thoracic pain, pleural effusion and superinfection.

To reduce the risk of pneumothorax or pulmonary hemorrhage during mediastinal biopsy, injection of small amounts of saline with a small-gauge needle can be used to distend the extrapleural tissue, which allows access to most mediastinal lesions, using an exclusive extrapleural pathway without transgression of the visceral pleura [33] (fig. 4). Similarly, extrapleural injection of saline displaces the pleura, allowing for a safe transpleural access to subpleural pulmonary lesions [34].

When a localization wire is placed, dislodgement of the harpoon is noticed in 3–10%.

Hemoptysis or hemorrhage is encountered in less than 10% of PTNB, most of which are not life threatening [18, 27, 29]. This complication can be impressive for the patient, but rarely requires specific treatment, as hemorrhage is almost always self-limited. A limited perinodular alveolar hemorrhage is commonly observed on CT and can obscure the nodule, rendering further punctures impossible with fluoroscopy control (fig. 1). Alveolar blood is usually not exteriorated. Codeine can be given to reduce cough. Other complications, such as mediastinal emphysema, thoracic wall hematoma, hemothorax, cardiac tamponade, empyema, bronchopleural fistula, lung torsion and implantation metastasis along the needle tract, air embolus and sudden death are rarely observed [35, 36]. Mortality rate of PTNB is estimated at 0.02% [19].

Clinical Usefulness of PTNB

A recent study on the influence of PTNB on treatment showed that management was altered in 51% of patients and unaltered (i.e. confirmed a diagnosis of a resectable malignancy or provided nondiagnostic results) in 49%. Surgery was avoided in 83% of biopsies that altered patient treatment [37]. When the pretest likehood of malignancy of a resectable lesion is high, thoracotomy is appropriate since preoperative PTNB or fiberoptic bronchoscopy (FOB) is unlikely to alter patient management [3]. Otherwise, PTNB and FOB must be considered complementary and PTNB performed only after a negative FOB. In indeterminate pulmonary nodules, VATS may be the method of choice, providing simultaneous diagnosis and treatment and reducing total cost (table 2).

Future Direction

The sensitivity of transbronchial needle aspiration (TBNA) for hilar and mediastinal malignancy varies from 34 to more than 90%, according to the experience of the operator and the equipment that is used [38–40]. Nevertheless, one large survey of chest physicians reported that only 12% routinely performed TBNA [41]. Virtual bronchoscopy (VB) is a 4D image reconstruction technique that produces simulated endobronchial images obtained from a spiral CT data set. Recent studies have achieved automatic matching between FOB and VB as a guidance to TBNA of enlarged hilar or mediastinal lymph nodes [40, 42]. Preliminary results show that merging of VB and FOB could improve the results of TBNA that are noted in the literature, even when small needles (22 G) are used [40].

Percutaneous Aspiration and Drainage of Thoracic Fluid Collections

Thoracic fluid collections of various origin, located in the pleura, pericardium, lung or mediastinum can be aspirated or drained percutaneously with imaging guidance. Percutaneous therapy is an important refinement compared to blind bedside technique and compares favorably with surgery. Diagnostic fluid aspiration includes cytological, bacteriological and chemical analyses. Confirmation of malignant cells, exsudative fluid, blood, lymph, bile, amylase, clear fluid or gross pus give etiological indications. Fluoroscopy, US and CT can be used as guidance modalities, either alone or in combination. The choice of the imaging technique depends on technical characteristics, availability, location of the collection and operator expertise. Loculated pleural effusions may be treated by thoracocentesis, thoracoscopy, surgically or CT-guided thoracostomy tube drainage, open drainage or thoracotomy and pleural decortication. Imaging guidance best insures proper catheter positioning.

Guidance Modalities

Fluoroscopy. Uni- or biplanar fluoroscopy is used for percutaneous drainage of large pleural and pulmonary collections [31, 43–50]. The patient is placed in a sitting or a posterior oblique position with the involved side up. A free pneumothorax is drained by a cephalad anterior approach, the patient being in the upright position. Pulmonary abscesses can be drained with fluoroscopy control when a broad contact with the pleura is demonstrated. When a catheter is inserted in a pulmonary or in a pleural collection with US or CT control, definitive adjustment of the tip of the catheter is easily achieved with fluoroscopy control [51]. For this purpose, we use a combined CT and angiography suite equipped by a single table, which pivots on a vertical axis. The patient is brought under fluoroscopy without moving in a few seconds [52]. Opacification of thoracic cavities is best documented with fluoroscopy.

Ultrasonography. US is particularly indicated to guide bedside percutaneous aspiration and catheter drainage of pericardial and pleural fluid, even of reduced amount [31, 44–46, 51, 53–56]. Pulmonary abscesses that are located in a subpleural location can also be included. Shifting of free pleural fluid during respiratory movements and change of the patient's position is easily observed with US. Percutaneous approach is performed in the position that optimally displays access to the fluid collection.

Computed Tomography. CT offers exquisite anatomical display of all thoracic structures and allows percutaneous access to all spaces with equal ease [31, 44–47, 51, 57–60] (fig. 4–8). Most catheters can be inserted, the patient remaining in a supine position. The optimal percutaneous entry point to a pulmonary abscess is defined according to its pleural contact, location of pleural fissures and vascular structures. CT is particularly useful for the percutaneous approach to the mediastinum, pleural fissures and for pulmonary abscesses with a reduced pleural contact.

CT is the optimal modality to confirm pneumothorax or pneumomediastinum following a percutaneous procedure.

Drainage Techniques

Number and size of percutaneous drainage catheters should be adapted to the number and extent of collections and to viscosity of fluid to be drained. Small 7F to 9F flexible catheters are well tolerated and sufficient for a short-term drainage of water-like fluid. The trocar technique is the most expeditive. It can be used in combination with the tandem technique (a trocar is inserted parallel to an 18-gauge needle placed in the collection for aspiration). This technique is useful for large collections and pulmonary abscesses with a broad pleural contact. The angiographic catheter exchange technique or Seldinger technique is more rarely used in the thorax and most suitable for mediastinal collections or small or encapsulated pleural pockets that are located in the paramediastinal pleural space [58].

Percutaneous access through a thickened pleura can be difficult, even when using regular chest tubes as stiff dilators and guide wires may be required. Chest drainage catheters are connected to a continuous negative water-seal suction. Gentle saline irrigation is performed on the ward to increase drainage and maintain catheter patency.

Pleural Empyema. Empyemas develop secondary to preexisting pulmonary, mediastinal or thoracic wall infection, spread of cervical or abdominal infection, trauma, surgical or other invasive thoracic procedures, lung abscess or arise from hematogenous spread of infection. Of the patients with pleural empyema, 50% have coexisting pneumonia. Clinical signs may be torpid. Time interval between onset of empyema and diagnosis may be several weeks. Antibiotherapy is necessary, but without effective fluid drainage, medical treatment will fail.

CT discloses satellite pleural pockets that form rapidly due to pleural adhesions and can be aspirated or drained with small-caliber catheters (fig. 5). Pleural fluid, encapsulated in a fissure, can also be adequately drained with CT control with or without transgression of collapsed lung

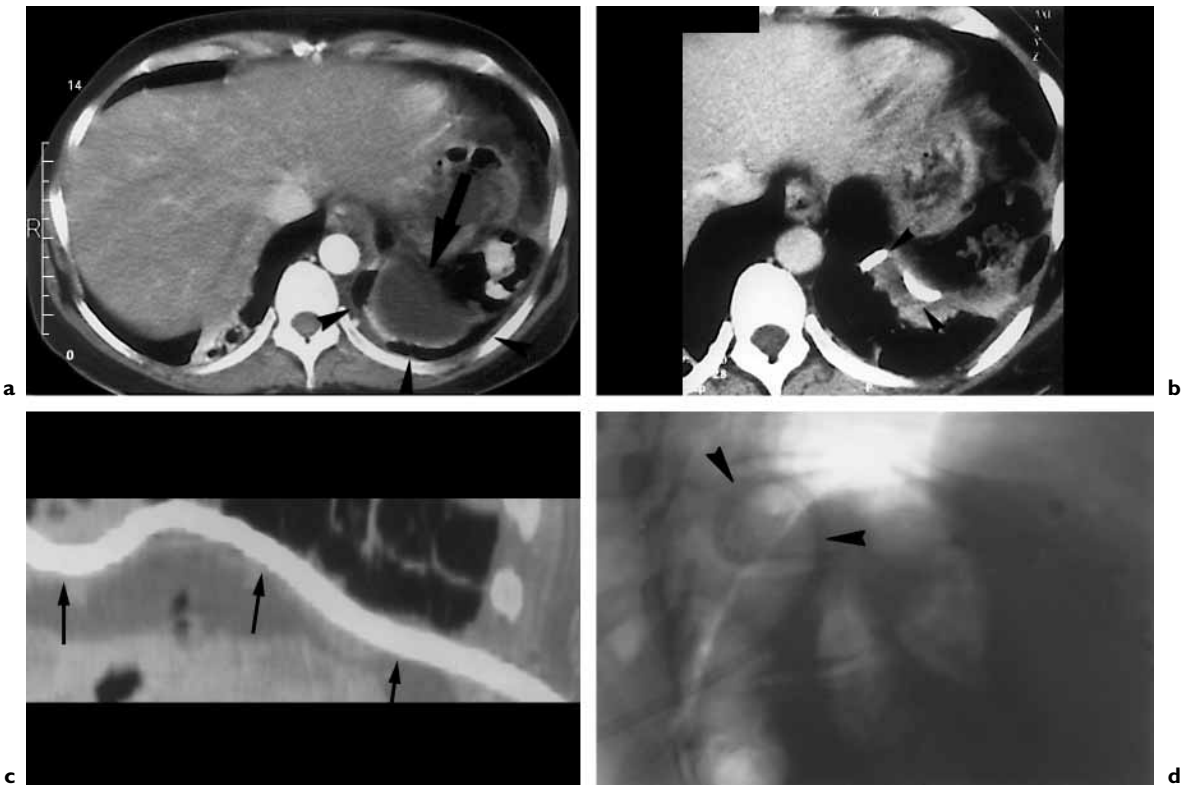

Fig. 5. Percutaneous drainage of a loculated empyema by an extrapleural pathway. **a** CT shows a left basal loculated empyema (arrow) following resection of the spleen, left adrenal and left kidney for invasive adrenal cancer. Note that the collection is surrounded by pulmonary parenchyma (arrowheads) preventing puncture in an axial plane. **b** A 9F pigtail catheter was inserted under combined CT and fluoroscopic guidance with an oblique extrapleural approach along the diaphragm. The curled pigtail tip of the catheter is documented inside the collapsed cavity (arrowheads). **c** Curved multiplanar reformatting along the catheter pathway (arrows) demonstrates its extrapleural position and the absence of lung injury. **d** Fluoroscopic view shows the extremity of the catheter coiling in the empyema (arrowheads).

parenchyma by the catheter. The diameter of the catheter varies from 7F to 30F according to the viscosity of the fluid.

Indications depend on the evolutionary stage of the pleural effusion [61] (table 3). Classes 1 and 2 or exsudative phase is an obligatory transitional phase before the empyema is formed and does not require drainage. Pleural effusion of Class 3 can still be treated by complete aspiration of the pleural fluid, but the recurrence rate is 75%. A collection of Class 4 or at the fibrinopurulent stage should be drained with mid-sized 8F to 14F catheters, whereas Class 6 effusions require regularly large bore 20F to 30F catheters. If drainage is attempted during Class 4, pleural thickening may increase to 10 mm within a week. At Class 6, fibroblasts infiltrate the thickened pleura and limit expansion of the underlying lung due to pleural peels.

Technical success is obtained in almost all cases. Multiple catheters are required in 30% of cases. Clinical success is achieved in 70–89% of patients (table 4) and depends on the stage of empyema. With a history of illness in excess of 1 month before drainage, the procedure may fail in spite of insertion of multiple catheters. Usually, duration of percutaneous drainage is about 1 week, although a single session catheter treatment was described [55]. Radiologically guided drainage procedures exhibit a similar efficiency in patients in whom previous surgical tubes have failed, as in patients treated in a first intent (table 5). Failure of percutaneous drainage varies from 12 to 28%: in chronic empyema, pleural thickening can prevent any closed catheter insertion. Failure of the pleural cavity to collapse and obliterate occurs in 5–12% and favors recurrence, which requires additional drainage. Opacification of the pleural catheter with propyliodine oil

Table 3. Classification and treatment of pleural effusions

Type of effusion	Class 1 non significant	Class 2 typical para-pneumonic	Classe 3 borderline complicated	Class 4 simple complicated	Class 5 complex complicated	Class 6 simple empyema	Class 7 complex empyema
Imaging aspect	<10 mm on decubitus chest X-ray free flowing	>10 mm on decubitus chest X-ray free flowing	usually not loculated	not loculated	multiloculated	single loculus or free flowing	multiloculated
Fluid aspect	clear	clear	clear	not frank pus	not frank pus	frank pus	frank pus
pH	>7.2	>7.2	>7.0 and <7.2	<7.0	<7.0		
Glucose, mg/dl	>40	>40	>40	<40	<40		
LDH, U/l	<1,000	<1,000	>1,000				
Gram stain or culture	negative	negative	negative	positive	positive		
Treatment	not indicated (antibiotics)	antibiotics alone (thoraco-centesis if ineffective)	antibiotics (+ serial thoraco-centesis)	antibiotics + thoracostomy catheter	thoracostomy catheter + thrombolytics (thoracoscopy if ineffective)	thoracostomy tube ± decortication	thoracostomy tube + thrombolytics ± decortication

Adapted from Light and Rodriguez [61].

Table 4. Percutaneous drainage of pleural empyema in a first intent

Authors	Patients	Calibre of drainage catheter french	Guidance modality	Duration of drainage days	Clinical success %
van Sonnenberg et al. [51]	17	8.3–12	CT: 59% US: 41%	–	88
Westcott [43]	12	8–10	fluoroscopy	1–7	83
O'Moore et al. [54]	17	8.3–12	US		88
Silverman et al. [46]	43	8.3–12	US: 70% CT: 18% fluoroscopy: 12%	7–45	72
Merriam et al. [45]	18	8–14	fluoroscopy CT, US	1–20 (9)	80
Hunnam and Flower [44]	20		fluoroscopy: 5% CT: 25%, US: 40% or combination: 30%	2–42 (9)	80
Reinhold et al. [32]	42	9–14	US: 72% CT: 20% fluoroscopy: 8%	–	80
Neff et al. [59]	10	8.4–14	US: 80% CT: 20%	4–18 (10)	83
Cummin et al. [55]	13	20–28	US	1	85
Dondelinger and Kurdziel [58]	14	8–24	CT	(12)	89
Lambiase et al. [50]	27	12–14	CT or US or fluoroscopy	3–33 (12)	70

Figures in parentheses are means.

can reveal unexpected bronchopleural fistulae. Massive bronchopleural fistulae are an indication for surgery.

Thick pleural peels often resolve spontaneously after weeks or months and regression can be followed by serial CT examinations. In selected patients, pleural decortication should only be considered if pleural thickening persists [59].

Irrigation and lavage are performed when blood or viscous material is present. Intrapleural injection of fibrinolytic agents was proven to be efficient in the prevention of fibrin deposit and secondary loculation of the empyema (classes 5 and 7 of Light) [47, 49, 61–75] (table 6). By reducing the number of pleural pockets, it also reduces the number of drainage catheters, length of drainage and hospitalization, and prevents progressive fibrosis of the pleural surfaces. Intrapleurally injected fibrinolytic agents do not diffuse through the pleura, and blood coagulation tests are not affected. Urokinase should be preferred to streptokinase to avoid possible allergic reactions. Recent surgical bronchial suture, macroscopic bronchopleural fistula and recent trauma should be considered as a relative contraindication of intrapleural injections of fibrinolytic agents [76]. Larger prospective studies are required to evaluate the effect of daily administration of intrapleural fibrinolytic agents on morbidity, mortality or the need for surgical intervention.

Table 5. Percutaneous drainage of pleural empyema in a second intent after failed chest tube drainage

Authors	Failure of thoracostomy tube	Clinical success
Merriam et al. [45]	7	4 (57)
van Sonnenberg et al. [51]	13	12 (92)
Westcott [43]	4	4 (100)
Silverman et al. [46]	3	3 (100)
Moulton et al. [47]	5	5 (100)
Lambiase et al. [50]	8	4 (50)

Figures in parentheses are percentages.

Table 6. Percutaneous drainage of pleural empyema and intrapleural injection of fibrinolytic agents

Authors	Patients	Fibrinolytic agents	Dose IU/day	Results %	Complications
Bergh et al. [62]	12	SK	250,000	83	low-grade fever
Berglin et al. [63]	10	SK		100	chest discomfort (3)
Fraedrich et al. [64]	27	SK		40	–
Moulton et al. [47]	13	UK	80–150,000	100	–
Lee et al. [49]	10	UK	100,000	90	–
Aye et al. [65]	14	SK	250,000	93	fever (3)
Henke and Leatherman [66]	12	SK	250,000	83	–
Robinson et al. [67]	13	SK (3)	150,000	77	fever (1)
		UK (10)	100,000		
Taylor et al. [68]	20	SK	250,000	95	fever (1)
Moulton et al. [69]	96	UK	250,000	94	–
Park et al. [70]	31	UK	250,000	81	–
Jerjes-Sanchez et al. [71]	30	SK	250,000	93	pain, fever, rash, neuro sign
Temes et al. [72]	26	SK	~ 275,000	62–70	bleeding (1)
			~ 120,000	62–70	fever, discomfort
Davies et al. [73]	12	SK	250,000	100	–
	12	saline	(control group)	75	–
Bouros et al. [74]	25	SK	250,000	92	fever, 28%
	25	UK	100,000	92	–
Chin and Lim [75]	23	SK	250,000	70	–
	29	–	(control group)	66	–

Most studies contain subgroups of patients who did not respond to drainage without the use of fibrinolytic agents. SK = Streptokinase; UK = urokinase. Figures in parentheses are number of patients.

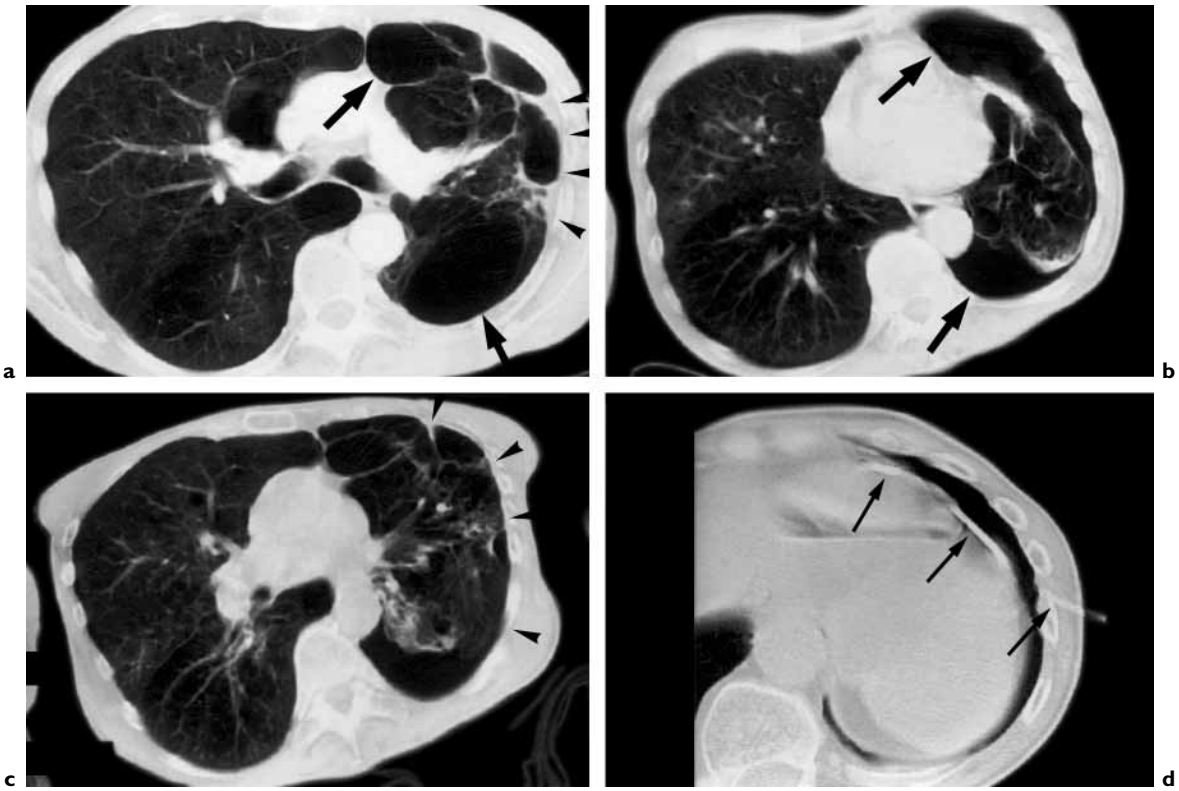

Fig. 6. Percutaneous drainage of a loculated pneumothorax. **a** A 70-year-old patient presented with severe acute dyspnea in the emergency department. CT performed 2 months before admission demonstrates severe COPD with large bullae on the left side (arrows) and pleural adhesions (arrowheads). **b, c** CT confirmed a loculated pneumothorax (arrows) in a subpulmonic location. Multiple pleural adhesions (arrowheads) discouraged from blind catheter drainage. **d** A 9F pigtail catheter was inserted under CT guidance in the anterior costodiaphragmatic sulcus. The air leak resolved after 5 days of drainage, but relapsed 1 month later. The procedure was repeated and subsequent chemical pleurodesis performed through the pleural catheter (arrows).

Malignant Pleural Effusion. Recurrent malignant pleurisies are usually drained with soft 8F catheters. Sclerosing drugs (doxycyclin, bleomycin) that limit mesothelial cell secretion are injected through the catheter when output volume has decreased to 100 ml or less per day. Obstruction of the pulmonary interstitium by metastatic lymphangitis can impede the lung to reexpand and is a contraindication to treatment. Complete regression of the pleural effusion is obtained in 61–81% and partial resolution in up to 95%, which is equal to response with larger thoracostomy tubes [48, 56, 77]. In 20–40% of patients, a pneumothorax 'ex vacuo' will appear, due to a stiff and noncompliant lung after chronic compression. In 50% of those patients, the lung will reexpand in the next days, but in 50%, air will persist until fluid has reaccumulated. Nevertheless, even in the latter situation, dyspnea can be dramatically improved.

Posttraumatic Hemothorax. Massive hemothorax should be drained to reduce compression of the underlying lung parenchyma and prevent encapsulation and adherences. Large bore catheters are mandatory and pleural lavage can be useful. In selected cases, careful angiographic workup is indicated, including catheterization of all potentially involved intercostal arteries, internal mammary and inferior phrenic arteries. Active arterial bleeding is treated by hemostatic embolization with gelfoam, polyvinyl alcohol particles, or coils.

Gazeous Collections. Postbiopsy or spontaneous pneumothorax can be drained percutaneously with small caliber catheters [30–32] (fig. 6). Evacuation of the pneumothorax is performed for patient comfort and safety or to continue PTNB if accurate localization of the lesion turns difficult. Most pneumothoraces can be connected to a Heimlich valve, and when recurrent chemically pleuro-

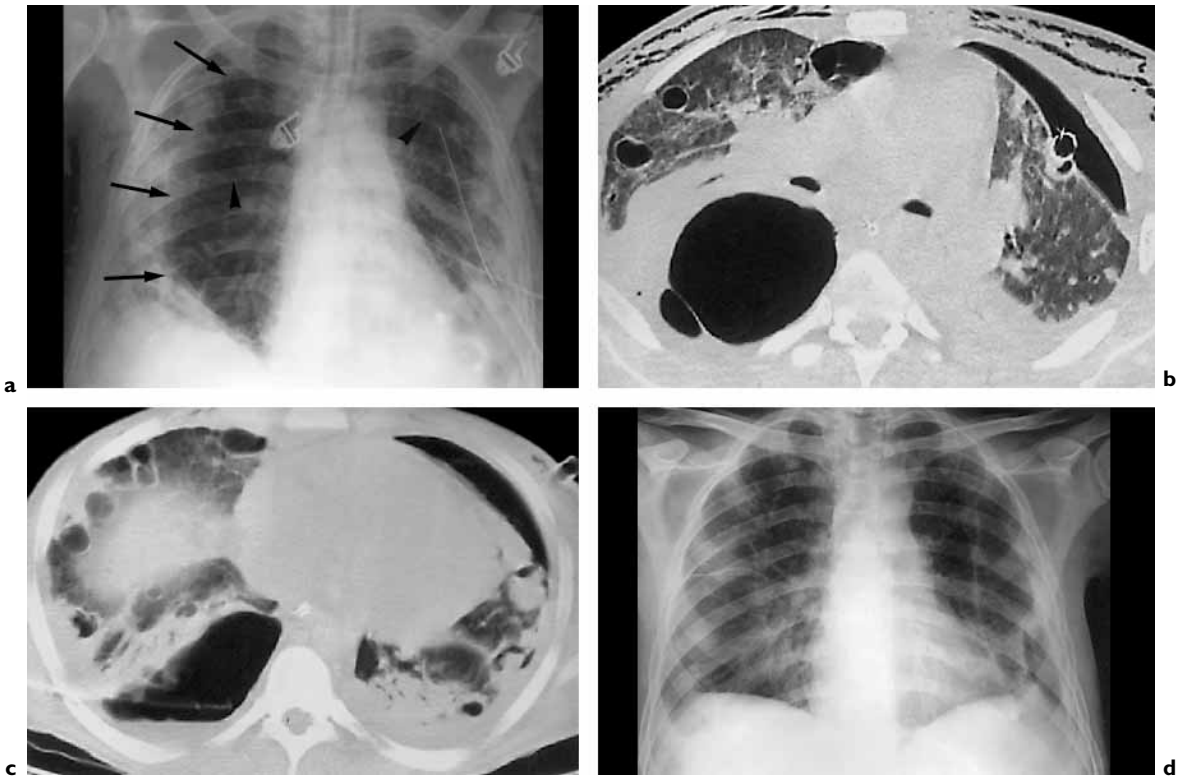

Fig. 7. Percutaneous drainage of a pneumatocele. **a** A 24-year-old intravenous drug addict presented with pulmonary staphylococcus infection following endocarditis. Recurrent left-sided pneumothorax was treated by multiple thoracostomy tubes. Severe respiratory failure developed along with a rapidly growing lung lucency (arrows) compressing the normal parenchyma on the right side. Note the multiple cavitated nodules (arrowheads) on both sides. **b** CT confirmed a large right posterior pneumatocele and a small left pneumothorax with well-positioned chest tubes. **c** A 9F pigtail catheter was inserted under CT guidance in the pneumatocele, which dramatically improved the patient's symptoms. **d** After 3 weeks of negative waterseal aspiration, a chest X-ray confirmed complete regression of the pneumatocele.

desed. Percutaneous drainage of pulmonary pneumatocele has also been described [78] (fig. 7).

Pulmonary Abscess. Pyogenic pulmonary abscesses occur rarely today, due to progress in antibiotic treatment and more efficient eradication of the cause. They are mainly seen in adults, whose general condition is debilitated by cancer, alcoholism, denutrition, diabetes and immune deficiency. Pulmonary abscess results from hematogenous spread, or from infection of a preexisting pulmonary cavity (emphysematous bulla, posttraumatic pneumatocele or pseudocyst, tuberculosis, fungus), or pulmonary infarction or tumor. A pulmonary abscess can complicate pneumonia with or without bronchial obstruction. A pulmonary abscess which resists medical treatment, postural and bronchoscopic drainage requires percutaneous drainage.

A percutaneous diagnostic aspiration with an 18-gauge needle can preceed catheter insertion in doubtful cases. Bullae may frequently contain an air-fluid level, but are not necessarily infected. An abscess with a diameter of 1–3 cm is adequately treated by a single percutaneous aspiration and antibiotics.

Endoscopical transbronchial placement of a catheter inside a lung abscess can be planned with CT and monitored with fluoroscopy control. Transbronchial drainage is less comfortable for the patient than a percutaneous approach. Contamination of the opposite lung is also a risk with the transbronchial technique. Mechanical ventilation is not a contraindication for percutaneous abscess drainage [79].

Pyogenic lung abscesses are often located in the periphery of the lung and usually they do not break through the lobar fissure. Pleural symphyses are rapidly established.

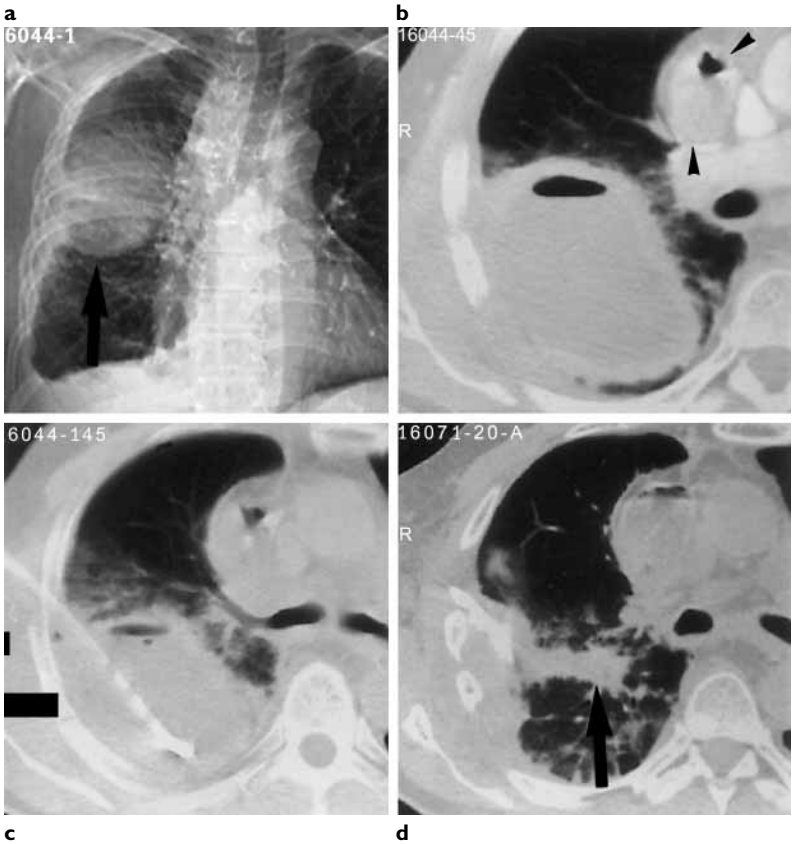

Fig. 8. Percutaneous drainage of pulmonary abscess. **a** A 51-year-old patient presented with a 7-cm pulmonary abscess (arrow) of the right upper lobe, following large bowel plasty for esophageal cancer. **b** CT confirmed a broad contact of the abscess with the pleura. The arrowheads show the large bowel plasty. **c** A 9F pigtail catheter was inserted under CT guidance and drained pus. **d** CT control on the next day demonstrated complete regression of the abscess (arrow).

The broad pleural contact allows planning of a percutaneous access in such a way, that normal lung parenchyma is not crossed by the drainage catheter (fig. 8). Pleural empyema by direct contamination is unlikely to occur when the trocar technique is used, and in practice, it does not make a difference if an empyema or a large lung abscess is drained. The trocar technique is the preferred drainage modality. Generally, 7F to 14F catheters are adequate. The drainage catheter is connected to a negative waterseal aspiration. Pulmonary abscesses have a more or less thick wall and do not collapse rapidly after aspiration. Duration of drainage is variable, the cavity may close only after 4 or 5 weeks. Decompression should be performed slowly in order to avoid rupture of a vessel or a so-called Rasmussen pseudoaneurysm that is incorporated or located close to the abscess wall. Lavage of a pulmonary abscess is dangerous due to the risk of bronchogenic spread of pus. Injection of contrast medium through the drainage catheter does not add significant information, but patency of the catheter should be maintained by daily injection of a minimal amount of saline. Daily chest radiographs are imperative for monitoring regression of the abscess cavity and early detection of complications.

Cure of the abscess is obtained in 73–100% of cases but overall mortality is high, due to a bad general condition or underlying disease [53, 57, 58, 60, 79–84] (table 7). Surgery remains indicated when extensive necrosis of lung parenchyma or life-threatening hemorrhage occurs. Temporizing percutaneous drainage cures the abscess, but surgery can be required for removal of necrotized tissue or pleural decortication.

Mediastinal Collections. Mediastinal abscesses result from circumscribed mediastinitis. Mediastinal abscesses are among the most challenging infections to treat, as prognosis of diffuse mediastinitis is poor. CT distinguishes diffuse infiltration of mediastinal planes from circumscribed abscess, but separation between acute mediastinitis and postsurgical changes can remain problematic in the early phase. Most purulent mediastinal collections result from trauma, either penetrating transthoracic injury or perforation of the esophagus. Thoracic and mediastinal surgery can be followed by mediastinal abscess formation, and other intra- or extrathoracic infections can also spread to the mediastinum.

CT is the most useful modality for diagnosis and planning of percutaneous drainage of mediastinal collections.

Table 7. Percutaneous drainage of pulmonary abscess

Authors	Patients	Guidance modality	Calibre of drainage catheter french	Duration of drainage days	Clinical success %
Vainrub et al. [80]	3	fluoroscopy	16–18		100
Lorenzo et al. [81]	3	fluoroscopy	18-gauge teflon sheathed needle	aspiration	100
Rami-Porta et al. [82]	13	–	repeat aspiration 5–30	15	100
Yellin et al. [83]	7	fluoroscopy	–	15	100
Parker et al. [53]	6	fluoroscopy	7–10	10–59	100
Rice et al. [79]	11	fluoroscopy	–	–	73
Ball et al. [57]	3	fluoroscopy, US, CT	8–12	19–24	100
Dondelinger and Kurdziel [58]	7	CT	8–14	12	43[1]
van Sonnenberg et al. [60]	19	CT	9–20	4–38	84
Ha et al. [84]	6	CT	8–10	7–18	83

[1] Four of 7 patients died from underlying disease after successful drainage.

Table 8. Percutaneous drainage of mediastinal abscess

Authors	Patients	Guidance modality	Calibre of drainage catheter french	Duration of drainage days	Clinical success %
Gobien et al. [87]	6	CT fluoroscopy	8.3–14	5–91 days (mean 35)	83
Meranze et al. [85]	8	fluoroscopy	8–12	2–4 weeks	88
Carrol et al. [86]	5	CT	–	–	100
Ball et al. [57]	4	fluoroscopy, US, CT	8–12	mean 28 days	100

Abscesses in the anterior mediastinum are drained by a parasternal approach avoiding the internal mammary vessels. Abscesses that are located in the middle and posterior mediastinal compartment are treated by a paravertebral and extrapleural approach. In selected cases, a percutaneous cervical descending approach following the pathway of the infection can be used [2].

Multiple catheters are often necessary and are placed either at both sides of the thoracic spine or the sternum or in the upper and in the lower part of the mediastinum. Conservative treatment is commonly applied to esophageal perforation [85]. An endoesophageal catheter can be inserted through the esophageal tear or in combination with a percutaneous drainage catheter placed at the site of leakage. When a fistulous tract is present between the mediastinal abscess and an empyema or a subphrenic abscess, percutaneous drainage of these collections may resolve the mediastinal abscess [86]. Only a limited number of patients with percutaneous drainage are reported [57, 85–87] (table 8). Cure can be obtained in 83–100%, in the radiological literature, which does not consider the 30-days mortality rate.

Other mediastinal fluid collections, such as pancreatic pseudocysts, pleuro-pericardial or bronchogenic cysts, infected tumor, lymphocele or hematoma can be aspirated or drained percutaneously (fig. 4).

Pericardial Fluid Collection. Diagnosis is confirmed with transthoracic or transesophageal US [88]. Causes of pericardial effusion include cardiac insufficiency, malignant tumors, postoperative effusion, pericarditis, hypothyroidism, connective tissue disease, trauma and others.

Percutaneous aspiration of pericardial fluid is indicated for diagnosis; percutaneous drainage prevents cardiac tamponade. Clinical signs of tamponade include dyspnea, tachycardia, compromised venous return and paradoxical pulse. Large amounts of pericardial fluid can be drained with CT control, sometimes with an atypical left anterolateral puncture, but most effusions are evacuated with US guidance, by a subcostal or a subxiphoid approach. The angiographic catheter exchange technique is mainly used, the initial puncture being performed with an 18-gauge or a 5F teflon-sheathed needle. A 5F to 7F pigtail catheter is placed in the pericardial space [89]. Technical success of the procedure and decompression of the heart is achieved in almost all cases, when the effusion is of sufficient amount. Duration of drainage is several days only. Chylopericardium can be difficult to drain and may need thoracic duct ligation or pericardectomy.

Percutaneous Drainage of Tension Pneumomediastinum. Tension pneumomediastinum results from barotrauma in patients with increased pulmonary resistance who are mechanically ventilated, with an elevated PAP and PEEP. Alveolar rupture results in interstitial emphysema that migrates to the mediastinum along the bronchovascular sheaths. When the mediastinal air fails to escape, due to adhesions or scarring, tension pneumomediastinum develops. CT shows unequivocally the air collection in the mediastinum. It mainly dissects the anterior mediastinal fat planes, compressing the mediastinal vessels and the heart. Compromised venous return, cardiac and respiratory insufficiency and anuria urge for rapid decompression. A left-sided pneumothorax is usually associated.

Usual treatment of tension pneumomediastinum is mediastinostomy. Percutaneous catheter drainage is an alternative emergency treatment. A soft 12F or 14F drainage tube can be inserted into the mediastinum behind the sternum with CT guidance by a left anterolateral percutaneous approach. Multiple sideholes are necessary to avoid catheter occlusion during negative waterseal aspiration. When a left pneumothorax is also present, the mediastinal catheter should be inserted before exsufflation of the pleural air collection. [90].

Complications of Percutaneous Catheter Drainage

Complications occur in approximately 5% and are mainly due to inadequate catheter insertion technique [43, 46, 51, 80, 81, 87]. Injury to an intercostal artery can produce a hemothorax or a hematoma of the thoracic wall. Life-threatening hemorrhage is rare, but can be observed following rupture of the wall of a pulmonary abscess, erosion of a branch of the pulmonary artery or transfixation of an internal mammary or mediastinal vessel by the catheter.

Pericardial drainage is prone to most of the clinically significant complications, such as hemopericardium with tamponade, dysrhythmia, pneumopericardium or superinfection. The thoracic catheter can be introduced erroneously in the subdiaphragmatic space, liver or spleen when crosssectional imaging is not used properly. When the catheter creates a communication between a pulmonary abscess and the pleural space, a secondary empyema or a bronchopleural fistula can be established.

When normal lung is crossed with a large bore catheter using the trocar technique, a pulmonary infarction can result. A pleural sinus tract through the chest wall can persist when the patient has undergone previous irradiation, but chest wall gangrene is rare. Transient bacteremia and hemoptysis can occur during catheter insertion. Pneumothorax is a potentially frequent complication, but can be avoided by proper crosssection imaging. Complications are best avoided by a proper planning of percutaneous approach with CT control. When fluoroscopy is used predominantly as a guidance modality for thoracic drainage procedures, the overall complication rate is as high as 20%, most being minor events.

Other side-effects include subcutaneous emphysema, local skin infection at the entry point of the catheter and discomfort during breathing, rib erosion, catheter leakage, bending, breakage and obstruction.

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Percutaneous Dilatational Tracheostomy

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Summary

Tracheostomies are elective procedures performed in already intubated patients in whom prolonged mechanical ventilation is expected. Surgical open tracheostomy – which is usually performed by a surgeon in the operating theatre – has been the procedure of choice for decades. More recently, percutaneous dilatational tracheostomy (PT) techniques – which are bedside procedures which can be performed by any trained specialist – are becoming increasingly popular. PT consists of percutaneous needle puncture of the trachea, followed by stepwise (Ciaglia technique, using dilators of increasing size) or one-time (Griggs technique, using dedicated dilator forceps) dilatation and placement of a tracheostomy tube. The indications of PT being similar to those of surgical open tracheostomy, the former seems to offer various advantages over ST, including logistic benefits (no need for an operating theatre and time, no need for patient transport, hence less time between the decision and performance of tracheostomy, and cost savings), and an equal or even better safety profile (less immediate and long-term complications). Necessary requirements for PT are a trained operator (which may be a surgeon or an ICU specialist) and assistants (probably including an experienced endoscopist for peroperative endoscopic control). PT is a safe bedside ICU procedure in experienced hands, and may – due to its relative simplicity, safety and bedside performance – influence optimal airway management strategies in the future.

Definition and History

Percutaneous dilatational tracheostomy (PT) is a bedside tracheostomy technique that consists of percutaneous needle puncture of the trachea, followed by stepwise or one-time dilatation and placement of a tracheostomy tube.

Tracheostomy is one of the oldest procedures in medical history. The earliest known references to tracheostomy are found in the ancient Hindu writings (circa 2000 BC) and in ancient Egypt, some 3,500 years ago. In the later half of the 19th century, during the diphtheria epidemic in western Europe, tracheostomy became widely used as therapy. The German Trendelenburg [1] was the first to describe the use of a tracheostomy tube with a cuff in 1870. Modern surgical tracheostomy was introduced by Jackson [2] in the early 1900s.

Standardization of the procedure, refinements in anesthesiologic techniques and recommendations for aftercare reduced mortality of surgical tracheostomy significantly. In 1943, during the polio epidemic, tracheostomy was proposed by Galloway [3] as a permanent access route to the lower respiratory tract to facilitate removal of secretions in polio patients with respiratory failure [3].

The introduction of polio vaccines decreased the number of surgical tracheostomies, but the application of tracheostomy for positive pressure ventilation immediately followed and was facilitated by the development and

growth of intensive care units (ICU). Although some technical aspects in surgical tracheostomy had evolved, the basic technique for performing tracheostomy in a patient requiring an artificial airway for mechanical ventilation had remained largely unchanged since the original description by Jackson. This, and the historically rather high complication rate, has led to the widespread idea that tracheostomy necessarily is a surgical procedure which should only be performed in an operating theatre.

Since 1957, however, various percutaneous tracheostomy techniques have been described which allow a tracheostomy to be performed rapidly, easily and safely at the ICU bedside. Sheldon [4] used a three-bladed cutting stylette. The use of the Seldinger technique was first reported in 1969 by Toy and Weinstein [5]. In 1976, Brantigan and Grow [6] reported a large series of elective cricothyroidotomy, and in 1985, Ciaglia et al. [7] published their experience with percutaneous dilatational subcricoid tracheostomy. Major modifications of this technique include the advocation of the use of flexible bronchoscopy through the endotracheal tube to avoid paratracheal insertion of the tracheostomy tube, and to verify tracheostomy tube placement, and the advocation (also by Ciaglia) to place the tracheostomy tube between first and second or between the second and third tracheal rings, rather than in the subcricoid space.

A different approach was described by Schachner et al. [8] in 1989: instead of the stepped dilator technique of Ciaglia, he used a dilating forceps over a guidewire for rapid stomal dilatation. Because of the observed high risk of complications, Griggs et al. [9] proposed the use of a modified pair of Kelley forceps fitted over a guidewire to perform rapid stomal dilatation.

Of these procedures, the progressive dilatation method described by Ciaglia currently is the most popular technique.

Indications

The indications for PT are the same as for classical surgical tracheostomy. Tracheostomies (whether percutaneous or surgical) are elective procedures performed in patients who already have been intubated with an endotracheal tube; advantages of tracheostomy in these patients, as compared with long-term endotracheal intubation, are increased patient comfort, decreased laryngeal injury, facilitation of nursing care, improvement in communication and oral nourishment, and provision of a more secure airway. Percutaneous tracheostomy therefore should not be used as an emergency airway management procedure [10].

The timing of tracheostomy is the subject of continuing debate in the literature, and will not be discussed here. Ultimately, the timing of tracheostomy will depend on the analysis of risks and benefits of maintaining the endotracheal tube versus performing the tracheostomy in the individual patient with his or her individual underlying disease. Recent data suggest, however, a trend in favor of early tracheostomy, which may even be enhanced by the availability of percutaneous tracheostomy techniques, which present logistic benefits and an equal or better safety profile than surgical tracheostomy [11]. Large-scale, randomized, prospective studies in a variety of ICU patient categories will be necessary to identify the optimal airway management strategy.

Personnel and Equipment

Minimal personnel requirements include a trained, experienced operator (surgeon, medical intensivist/pulmonologist (see Discussion on who should perform PT) and an assistant for endotracheal tube handling, patient sedation and monitoring, and ventilatory and oxygenation requirements. This assistant, who stays at the head of the patient, can be a critical care fellow or anesthesiologist. This assistant, when qualified, may also perform fiberbronchoscopic control, although it is probably safer to leave endoscopic control to a third assistant (pulmonologist or qualified anesthesiologist). All medical personnel performing PTs should be proficient in airway management and be capable of managing acute airway complications.

Sufficient sedation and analgesia usually can be achieved by temporarily increasing usual intravenous maintenance drugs used in ventilation patients (e.g. fentanyl, midazolam, propofol). If needed, short-acting neuromuscular blockade (e.g. with atracurium) may be necessary.

A laryngeal mask airway may be used for ventilation, avoiding contact with or damage to the endotracheal tube during PT. This technique, however, is not recommended in obese patients, in those with high airway pressures or a high positive endexpiratory pressure, or in those at risk of vomiting.

In most adult patients, a size 8 or larger tracheostomy tube can be placed. Adjustments in tube length or configuration may be necessary in individual cases to ensure proper fit. Commercially available PT kits offer curved dilators (Cook Inc, Bloomington, Ill. USA) or straight

dilators (SIMS Inc., Keene, N.H., USA). The latter kit already includes a dedicated tracheostomy cannula which is sufficiently flexible and features a tapered distal tip. When using the curved dilator set, a tracheostomy cannula, flexible enough to be placed over the dilator, and preferably with a conical tip, is to be preferred (e.g. Shiley PERC; Mallinckrodt Inc, St Louis, Mo., USA).

When using the rapid dilation technique (SIMS Portex Ltd, Hythe, UK) a tracheostomy cannula is included in the kit.

Technique

PT is performed in a supine, adequately anesthetized, ventilated and oxygenated (F_iO_2 1.0) patient in the ICU, under continuous heart rate and oxygen saturation monitoring. The patient is positioned with the head extended and with a cushion under the shoulders. After careful identification of the thyroid and cricoid cartilage, the operative area is prepared (fig. 1).

Fig. 1. Prepared operative area (cranial view) with incision line above the second tracheal cartilage interspace (superior line), sternal notch (shorter curved line) and sternal midline (vertical line) marked.

The assistant (respiratory therapist, anesthesiologist) loosens the fixation system of the in-place endotracheal tube, deflates the cuff and adapts ventilator conditions as necessary to compensate for air leak, or uses an ambubag to insure ventilation and oxygenation. The endotracheal tube is then gently withdrawn (under direct visualization using a laryngoscope, or via flexible bronchoscopy) with deflated cuff until the tip of the latter is repositioned just below the vocal cords. The assistant should hold the loosened endotracheal tube firmly throughout the procedure to prevent inadvertent premature extubation.

Meanwhile, the operator makes a 1.5–2-cm horizontal skin incision above the first or second tracheal cartilage interspace, most often after additional local skin and subcutis anesthesia with 2% lidocaine.

While the left hand of the operator stabilizes the trachea, a 12- or 15-gauge needle is inserted at the anterior midline (fig. 2a), preferably under flexible bronchoscopic observation by a third assistant (pulmonologist or ICU specialist), thus avoiding paratracheal needle insertion or endotracheal tube and cuff damage. It is recommended, however, that the bronchoscope should only be inserted temporarily during the procedure, in order to avoid decreased minute volumes or hypercarbia. Free air bubbles are aspirated into the syringe when the tracheal lumen is reached; lidocaine is then injected into the tracheal lumen to decrease irritative cough reflexes in the course of the procedure. A flexible, curved guidewire (0.052 J) is gently introduced through the needle (fig. 2b and 3a). The correct intrabronchial distal orientation of the guidewire is confirmed by the bronchoscopist. The needle is then removed, and one of the two following techniques can be used.

Progressive Dilatation (Ciaglia) Technique

A standard PDT kit (Cook), using curved dilators, or straight dilators (SIMS Inc.) (fig. 2) [4] are used.

An 8-french guiding catheter is introduced into the trachea over the guidewire. When using the curved dilators, dilatations are done over this 'double guide' to prevent any kinking which may cause tissue trauma. The straight dilators are introduced over a 90°C angle to the trachea and advanced with a rotating movement until a band mark is reached. Dilatation usually starts with a 12-french dilator, positioned accurately according to the guiding marks. The whole assembly of guidewire, guiding catheter, and dilator are advanced as a unit to the skin position mark on the dilator (fig. 2c).

Dilators of increasing size are then inserted and removed going up to 36 fr for insertion of an 8-mm internal diameter single cannula tracheostomy tube. Slight overdilatation ensures easier passage of a 6-, 7- or 8-mm tube.

The tracheostomy tube is preloaded and positioned on the proper-sized lubricated dilator (18 fr for 6-mm ID tube, 21 fr for 7-mm ID tube, 24 fr for 8-mm ID tube, 28 fr for 9-mm ID tube). Its cuff should be actively deflated and well lubricated. The appropriate dilator

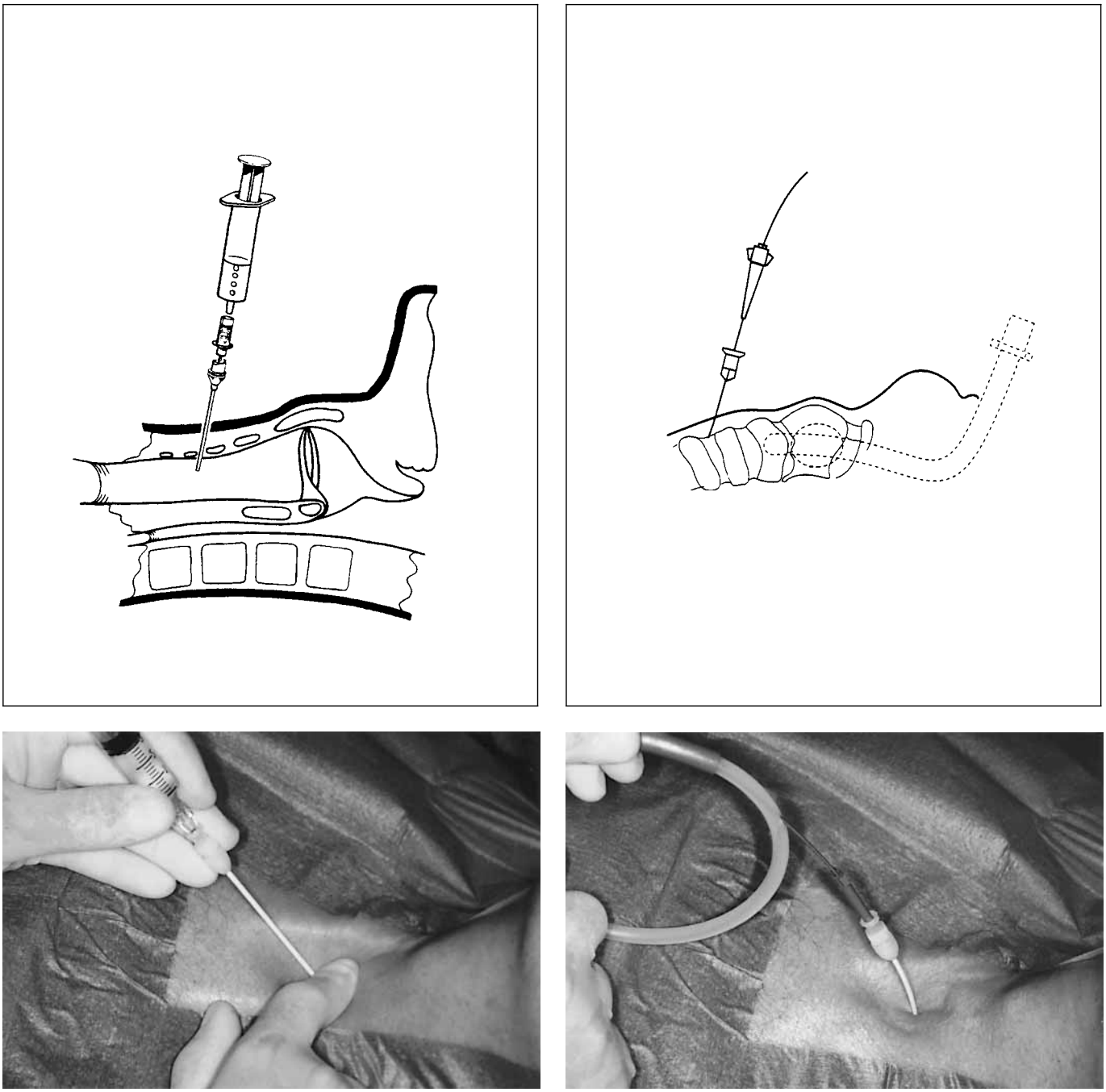
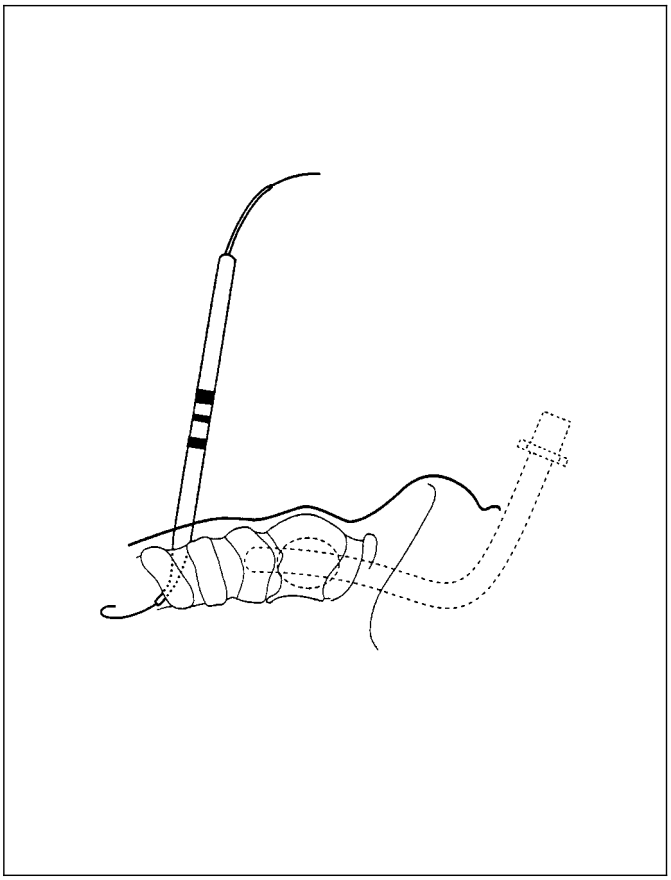
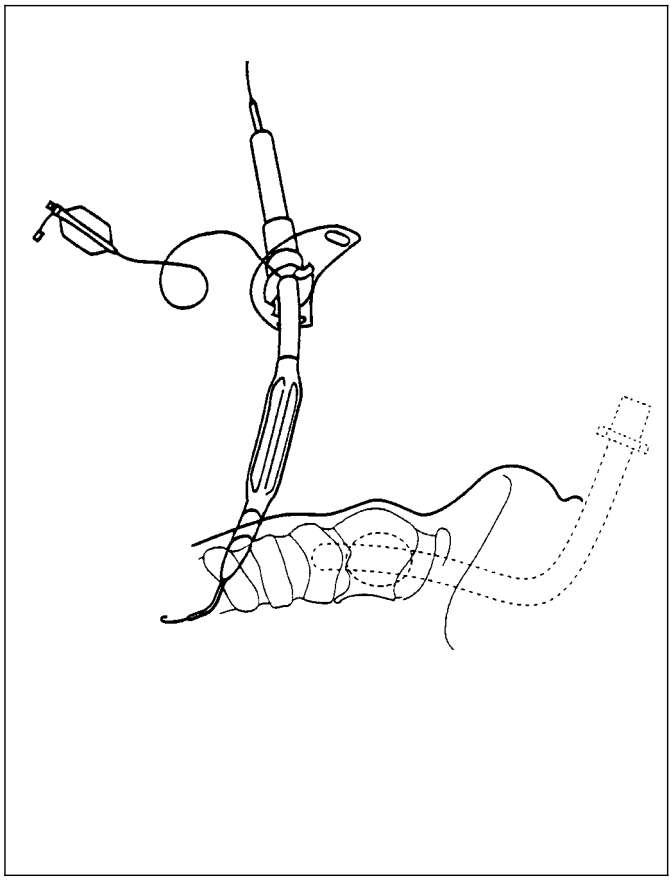
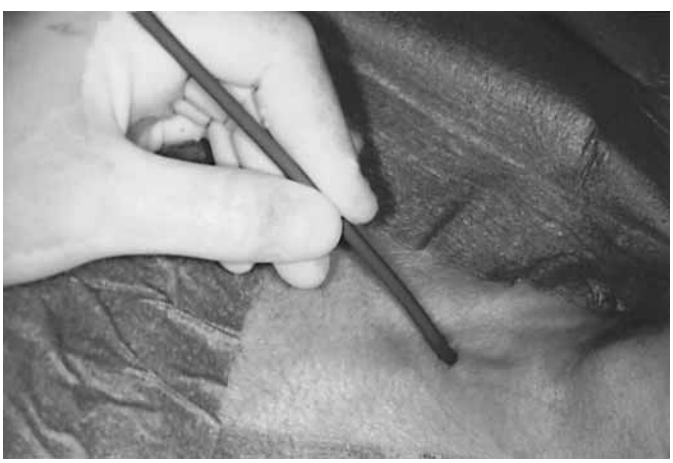


Fig. 2. Schematic and photographic illustration of the progressive dilatation-technique (Standard PDT kit; Cook). **a** The needle and cannula (with syringe attached) are inserted in the tracheal midline, into the insertion site. Air bubble aspiration confirms intratracheal position. Fiberbronchoscopic control confirms midline position. **b** After syringe removal, the guidewire introducer is inserted into the cannula; the guidewire is fed out of its sheath until at least 10 cm lie in the trachea. The cannula is then removed, leaving the guidewire in place. Distal orientation and intraluminal position of the guidewire may be confirmed endoscopically. **c** After advancing a guiding catheter over the guidewire, dilators of increasing diameter are advanced over the guiding catheter, and into the trachea. The guidewire, guiding catheter and dilator are advanced as a unit up to the skin position mark on the dilator. **d** The tracheostomy tube with the obturator/dilator is inserted into the trachea.







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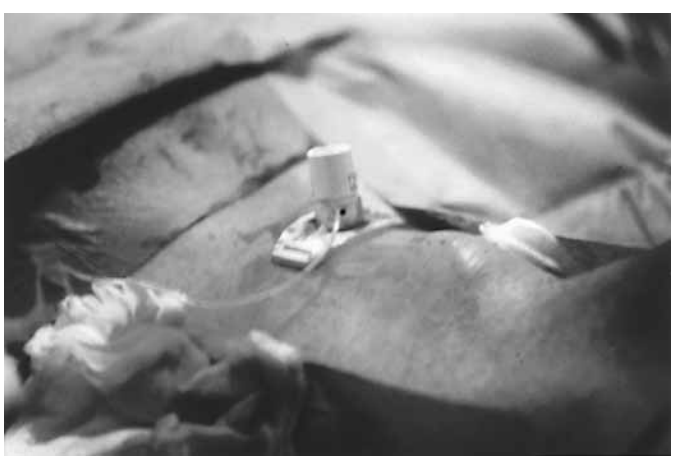

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carrying the tracheostomy tube is threaded over the double guide to the proper position (guiding marks), and the assembly is inserted as a unit into the trachea up to the flange of the tracheostomy tube (fig. 2d). During each dilation, bronchoscopic confirmation may reassure the operator.

After insertion of the tracheostomy cannula and after final bronchoscopic control, the guides and dilator are removed. Finally, the endotracheal tube is removed. Fiberbronchoscopic examination via the tracheostomy then controls the position of the tip of the tracheostomy cannula and allows for a bronchial toilette with aspira-

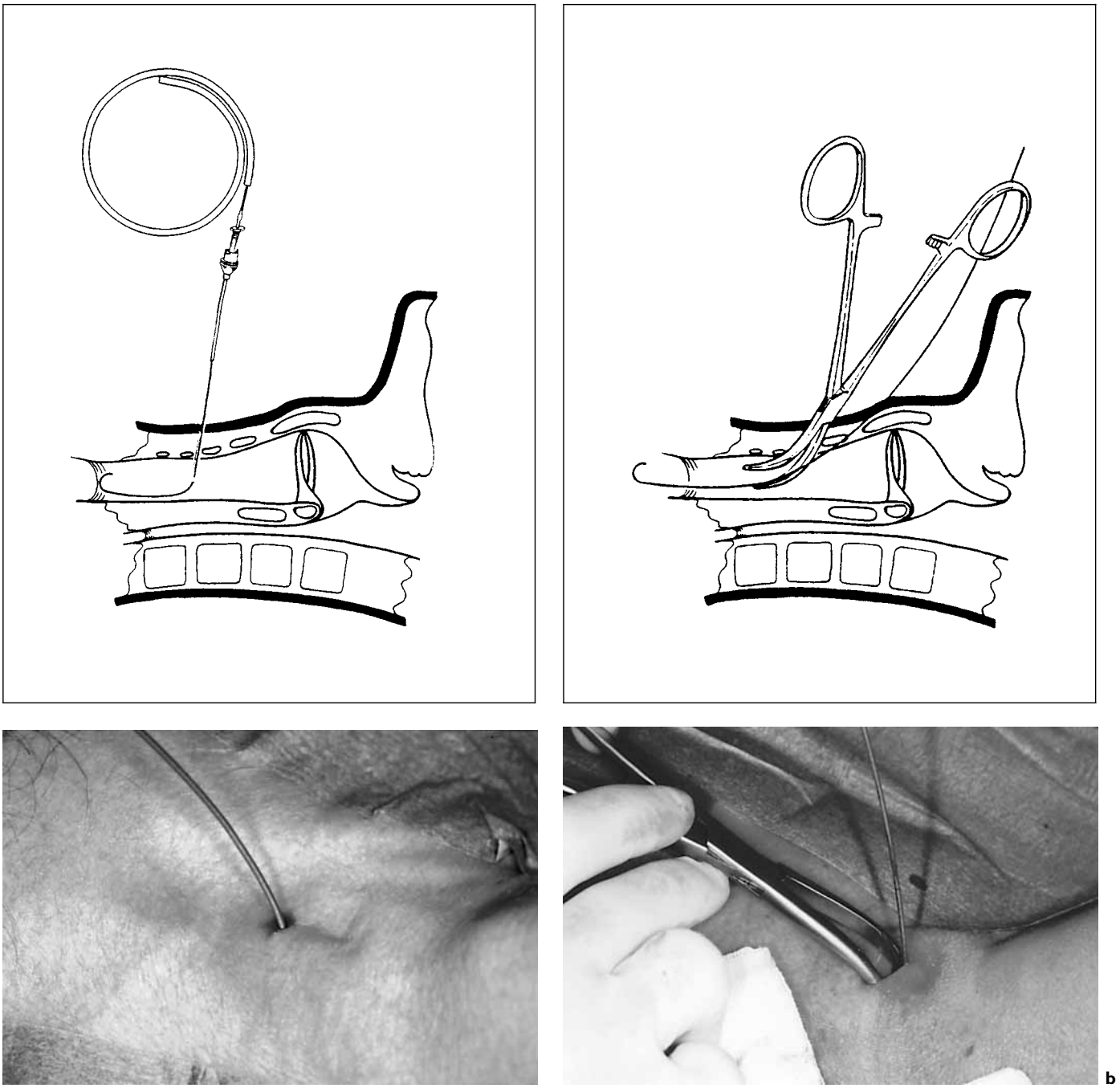
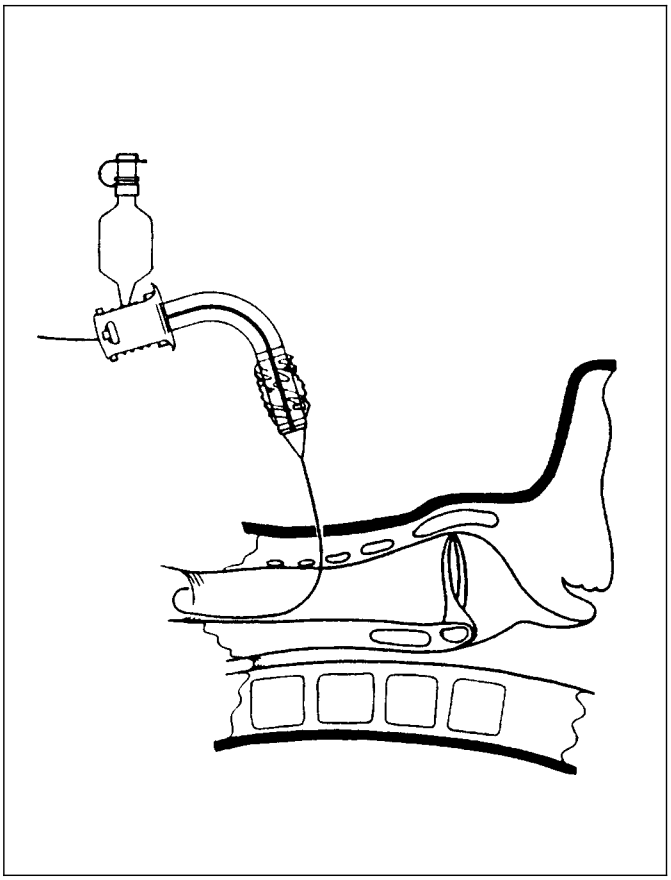


Fig. 3. Schematic and photographic illustration of the rapid dilatation technique (SIMS portex Ltd.). **a** After syringe removal, the guidewire introducer is inserted into the cannula; the guidewire is fed out of its sheath until at least 10 cm lie in the trachea. The cannula is then removed, leaving the guidewire in place. Distal orientation and intraluminal position of the guidewire may be confirmed endoscopically. **b** After endoscopic confirmation of correct introtracheal position, the forceps is gradually opened, dilating tissues sufficiently to accept the tracheostomy tube. The forceps is then withdrawn in the opened position. **c** The obturator and tracheostomy tube are passed over the guidewire into the trachea.



c

tion of blood clots. The tracheostomy cannula is secured, and local antibacterial ointment dressing may be applied to the stoma. Immediately after insertion of the tracheostomy cannula, manual bag ventilation with 100% oxygen via the cannula may alleviate occasional hypoxia.

In experienced hands, the whole procedure takes about 5 min (from the first needle puncture or incision, until the tracheostomy tube is in place). A chest radiograph after the procedure is recommended to detect the presence of any pneumothorax, pneumomediastinum, aspiration or atelectasis (e.g. by blood clots) or any other pulmonary abnormality resulting from the intervention.

Rapid Dilatation (Griggs) Technique

The dilating forceps originally described by Schachner (Rapitrach) no longer being marketed, the use of the commercially available Portex kit (SIMS Portex, SIMS Portex Ltd.), using Griggs technique is described (fig. 3) [9].

The dedicated percutaneous tracheostomy tool (a guidewire dilating forceps) is guided over the metal wire. It is introduced through the anterior tracheal interspace (its correct introtracheal position can be confirmed by flexible bronchoscopy through the endotracheal tube) and opened gently to dilate the tracheostomy site, and sufficiently to accept the tracheostomy tube (fig. 3b). The dilating forceps is removed, and the selected tracheostomy cannula, fitted on a snug plastic trocar, is placed over the guidewire into the trachea with deflated cuff, again under bronchoscopic control (fig. 3c).

The trocar and guidewire are removed, the cuff inflated, the endotracheal tube withdrawn and the tracheostomy cannula secured.

Although less widely used, this technique is equally safe (and may even be performed more rapidly) as compared to the Ciaglia technique.

Contraindications

Skin infections, unstable cervical vertebrae and increased intracranial pressure are absolute contraindications for PT (table 1). Relative contraindications (i.e. PT may be technically feasible, but is not accepted as first-line treatment of choice) include emergencies, high ventilatory requirements, tracheostomy in children, uncorrectable coagulopathies or the presence of anatomic abnormalities (e.g. goitre) or marked obesity. Anticoagulant therapy should be discontinued 3 h before the procedure. Thrombocytopenia or other coagulation disorders (e.g. disseminated intravascular coagulation) should be corrected with platelet or plasmatic substitution, respectively.

Table 1. Contraindications for PT

Absolute
Active infection at the anterior neck
Previous major surgery or gross distortion of anatomy (e.g. goiter, tumor)
Unstable cervical vertebrae
Relative
Increased intracranial pressure
Children < 15 years
Emergency situations
Bleeding diathesis
Previous minor neck surgery
Obesity and/or 'difficult' neck (extremely obese or extremely long)
High ventilatory/oxygenation requirements

Table 2. Complications of PT

Procedural
Bleeding
Paratracheal insertion
Tracheal wall tear or rupture
Tracheoesophageal fistula
Barotrauma
Hypoxia, Hypercarbia
Loss of airway
Death
In situ
Bleeding
Stomal infection
Tube displacement/early decannulation
Tube obstruction
Cuff leackage
Tracheal erosion
Tracheoesophageal fistula
Atelectasis
Death
Postdecannulation
Cosmetic deformity
Subglottic/tracheal stenosis
Tracheal granuloma
Tracheomalacia
Voice change

Results and Complications

Minimal bleeding during the procedure is almost always observed, and usually can be controlled with gauze sponges. If bleeding is more than expected, rapid termination of the procedure is warranted, since the tight fit of the tracheostomy cannula usually will tamponade the bleeding. If oozing persists, injection of some lidocaine with epinephrine around the stoma may be helpful and rechecking of the coagulation parameters is indicated.

Aspiration of bloody secretions from the airways is common, but should subside within 24–48 h.

Other reported, but rare short-term complications of percutaneous tracheostomy include major hemorrhage requiring blood transfusion, mucosal lesions of the trachea, submucosal tunnelization of the tracheal wall, perforation of the posterior tracheal wall with ensuing tracheoesophageal fistula, damage to the endotracheal tube or fiberbronchoscope, paratracheal insertion, barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema), stomal infection and difficulty in tube change after early dislodgement (table 2).

Theoretical advantages of percutaneous dilatational techniques over standard surgical tracheostomy procedures include the smaller skin incision with less devitalization of tissue, the reduced risk of major hemorrhage, infection, late sequelae (e.g. subglottic stenosis), less cosmetic deformity, its bedside performance reducing the logistic problems of transport of critically ill patients to the operating room and the search for operating room availability (thereby reducing cost and time between the decision to perform tracheostomy and the procedure itself) [12], although surgical tracheostomy is also performed as a bedside procedure in many centers [13]!

Comparing outcome of PT to open surgical tracheostomy on the basis of historical data, however, is biased by the fact that outcome reports on surgical tracheostomy (overall morbidity varying from 6 to 66% and mortality from 0 to 5%) are 20–30 years old and deal with non-ICU or mixed populations [13, 14].

Complication rates in large retrospective PT series [12, 15–20] compared favorably with those of open surgical tracheostomy: hemorrhage requiring transfusion occurred in less than 1% of patients and generally was confined to patients with a bleeding diathesis. Pneumothorax occurred in 0–4% of patients, whereas stomatitis requiring antibiotic therapy occurred in 1–2% and late subglottic stenosis in 0–1%, which seemed to be lower than after surgical tracheostomy.

As explained before, however, only prospective, randomized trials enable meaningful comparison between percutaneous and open surgical tracheostomy procedures. Until now, four such prospective comparative studies have been performed.

In 1991, Hazard et al. [21] reported the results of a study that randomized 46 mechanically ventilated patients with respiratory failure to either conventional operative tracheostomy or PT. Operative tracheostomies were performed in either the ICU or the operating room, under either local or general anesthesia by experienced board-certified surgeons. All of the percutaneous tracheostomies were performed under local anesthesia and intravenous sedation at the bedside in the ICU by or under the supervision of one of the investigators. Hemorrhage, infection and pneumothorax were the commonest early adverse events in both groups. These complications occurred significantly more commonly in patients who had operative tracheostomies (45.8%) than in patients who had percutaneous tracheostomies (12.5%). Delayed stomal healing, significant subglottic stenosis and cosmetic deformities were significantly commoner after operative tracheostomy (88%) than after percutaneous tracheostomy (27%). In summary, percutaneous tracheostomy was associated with a lower rate of both early and late adverse events compared with operative tracheostomy.

In 1995, Crofts et al. [22] published the results of a prospective clinical trial in which they randomized 53 critically ill mechanically ventilated patients to either open or percutaneous tracheostomy. Open tracheostomies were performed in the operating room by consulting surgeons, whereas percutaneous tracheostomies were performed in the ICU by supervised otolaryngology housestaff. The frequency of tracheostomy complications occurring during a 2-week follow-up period was low in both groups. There were no significant differences in the incidence of hemorrhage or other complications between the groups. The only stomal infection occurred in the open tracheostomy group.

In 1996, Friedman et al. [12] randomized 53 patients to either PT performed in the ICU by 1 of 2 intensivists or to open tracheostomy performed in the operating room by 1 of 4 surgeons. All PTs were performed under local anesthesia and intravenous sedation, whereas the open procedures were performed under general anesthesia. There were no significant differences in the rates of intraprocedural complications (35 vs. 41%; PT vs. open tracheostomy, respectively). However, postprocedural complications (accidental decannulation, bleeding, or stomal infection) occurred significantly more frequently in patients randomised to open tracheostomy (12 vs. 41%; PT vs. open tracheostomy, respectively). It was noted that the PT tracheostomy tubes appeared securer. Only 1 patient in the PT group experienced premature decannulation versus 4 patients in the open tracheostomy group. Despite the presence of retention sutures in the patients with surgical tracheostomies, the tracheostomy tube could not be reinserted in 2 of the 4 patients who experienced premature decannulation, resulting in death of both.

In a recent preliminary report, Heikkinen et al. [23] randomized 40 patients to PT or open tracheostomy. All tracheostomies were performed at the bedside under local anesthesia and intravenous sedation. There were no significant differences in complication rates between the two groups, except that the PT group required more intravenous sedation because 'the guidewire irritated the trachea' (probably because no lidocaine was injected into the tracheal lumen).

Discussion

It should be clear now, that PT techniques are swift and safe procedures in experienced hands, with a risk of early and late complications equal to or lower than that of open surgical tracheostomy.

Furthermore, since PT is a bedside technique, obviating the need for transportation of critically ill patients, and reducing the treatment delay and costs [24, 25], it may well represent the preferred technique for elective tracheostomy in critically ill patients, and may even change our general approach to tracheostomy in the ICU patient.

However, as for all new 'simplified' techniques, especially when available for surgeons as well as for non-surgical specialists and thus situated in the 'grey zone' between surgery and medicine, controversies and discussions – sometimes emotional or ill-based – arise. Similar controversies have taken place when fiberoptic or rigid interventional endoscopic techniques in bronchology and gastroenterology were developed, and are still taking place in thoracoscopy and, to a lesser extent, in the field of interventional bronchoscopic procedures.

Surgeons, obviously, state that tracheostomy – whether percutaneous or open – is a surgical procedure, and that whoever performs a procedure should be able to handle the emergent complications associated with it.

Although intrinsically logic, this statement would imply that, e.g. no cardiologist would be allowed to perform coronary balloon angioplasty, no pulmonologist would be allowed to perform laser therapy in the airways, no nephrologist would be allowed to perform a renal biopsy, and no gastroenterologist would be allowed to perform a polypectomy in the colon.

Inversely, however, no cardiologist would be allowed to treat cardiac arrhythmia after coronary surgery, no pulmonologist would be allowed to diagnose and treat postoperative (ventilator-associated) pneumonia, no gastroenterologist would be allowed to dilate postoperative anastomotic digestive stenosis, and no nephrologist would be allowed to take care of postoperative renal insufficiency. Protectionist reflexes should never interfere with a key element in the success of any medical or surgical act: teamwork. As to the tracheostomy discussions, surgeons are correct when they state that a lost airway can result in death within minutes, that – as a result – there is no time to call for back up, and that the 'procedurist' therefore should be able to perform emergency airway procedures. As proven by the various large patient series published by nonsurgical ICU specialists, they are not correct when saying that only surgeons can possess these qualifications.

It should be obvious, however, that any physician (surgeon, anaesthesiologist, medical intensivist) performing PT should have expertise in all aspects of airway management, including intubation, bronchoscopy and cricothyroidotomy. Credentials for PT should have the same requirements as for any (surgical) procedure: formal training, an apprenticeship and ongoing peer review. Experience in open surgical tracheostomy per se should not be a substitute for formal training and apprenticeship in PT because the procedures are similar.

Far better still than these 'pro-con' discussions on who should perform PT, would be to stimulate local active cooperation between the various specialists at the ICU bedside, the specification of which may differ from institution to institution. In our hospital for instance, PT is performed by a surgeon, endotracheal tube handling, ventilation and oxygenation are controlled by an anesthesiologist, and per- and postoperative bronchoscopic control is performed by a pulmonologist. In our opinion, this cooperation – when feasible – represents the best guarantee for optimal therapeutic outcome.

Although four [12, 21–23] prospective comparative studies have proven PT to be equal and in some aspects even superior to classical open surgical tracheostomy, some issues of concern or criticism remain.

PT might be associated with an increased risk of late tracheal stenosis because it is generally performed at a higher tracheal interspace than is open tracheostomy. However, when symptomatic tracheal stenosis has been observed after percutaneous tracheostomy, preexisting pathology of the airway – a recognized risk factor for the development of tracheal stenosis after open surgical tracheostomy – was invariably present. Retrospective and prospective studies, however, showed that late stenosis actually is less often observed after percutaneous than after operative tracheostomy [18–20]. Risk factors for this late complication include preexisting laryngotracheal damage (e.g. due to long-standing endotracheal intubation) and lack of experience with the PT procedure.

Fiberbronchoscopic control during the PT procedure can reduce minute ventilation and cause hypercapnia. This complication can easily be avoided by introducing the bronchoscope intermittently only during certain critical stages of the procedure (e.g. during endotracheal tube retraction, needle introduction in the trachea, guidewire passage, dilator introduction and cannula position control), by using a small-diameter bronchoscope (e.g. pediatric size), and by avoiding continuous suction through the bronchoscope. When these precautions are taken, we (and others) have never been confronted with hypoxemia, hypercarbia or dynamic hyperinflation.

The fear for paratracheal insertion, which has been supported by cadaveric studies, is inherent to a blind procedure such as PT. However, although not universally advocated by experienced surgeons or intensivists, fiberbronchoscopic control essentially eliminates this potentially life-threatening complication [26].

In our opinion, therefore, although it may increase the cost and logistic complexity of the procedure, fiberbronchoscopic control during the critical stages of percutaneous tracheostomy should be highly advocated.

The reduced logistic complexity of a bedside procedure is another major advantage of percutaneous tracheostomy (although surgical tracheostomy may also be performed at the bedside, many surgeons prefer the facilities of the operating theatre). Bedside PT thus avoids the potentially dangerous time- and personnel-consuming patient transport to the operating room. Furthermore, the treatment delay (i.e. the time between the decision to perform tracheostomy and the actual performance) has been shown to be substantially reduced (from 100.4 to 28.5 h) in patients randomized for PT as compared to those randomized to open surgical tracheostomy [12]. The simplicity of PT also leads to significantly reduced operating time: both set-up and actual procedural times with PT average one third of those with open tracheostomy.

Although increased speed in itself probably is not of primal concern [13], it is obvious that, if two procedures are equally safe or if the faster procedure is associated with a lower risk of complications, speed certainly is not disadvantageous [11].

Nevertheless, considerable variations in PT performance times have been observed, probably relating to the skill of the operator or individual patient characteristics (e.g. obese patients, short neck).

Again, mainly due to its relative simplicity and bedside performance, PT has been claimed to be less costly than open surgical tracheostomy. Several studies, North American as well as European, have estimated true costs and charges for PT to be approximately 50% of those of open tracheostomy. Cost savings are largely due to elimination of operating room charges and largely overcome the cost of the disposable kit, bronchoscopy and second/third assisting physician inherent to the PT procedure.

Although an open surgical tracheostomy procedure performed at the bedside probably would be the least expensive method of performing tracheostomy, current practice in the vast majority of hospitals where open surgical tracheostomy is performed in the operating room, undoubtedly makes PT the most cost-effective method.

Acknowledgment

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Emergency Transtracheal Oxygenation Techniques and Long-Term Transtracheal Oxygen Therapy

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Summary

Maintenance of adequate gas exchange and protection of the airway against aspiration of gastric content are the main goals of the anesthesiological and emergency management of the difficult airway. Meanwhile, there are accepted guidelines and algorithms for a rational approach to this problem and a variety of techniques and equipment has been evaluated and approved for this purpose. Among specially developed equipment that may help to visualize the larynx or to introduce endotracheal or pharyngeal tubes and analogous devices, transtracheal puncture remains an important route for oxygen application in the 'cannot intubate – cannot ventilate' scenario. This method has to be considered if any of the transoral accesses turns out to be not feasible and less invasive techniques have failed, or are not indicated. The optimal place for transcutaneous puncture is located right above the upper margin of the cricoid cartilage and midline position, since the cricothyroid membrane is nearly completely free of vessels and can be punctured without a high risk for bleeding, unless a clinically relevant coagulopathy is present. There are two different categories of nonsurgical transtracheal equipment: (1) transtracheal puncture with narrow cannulas and catheters that do not require initial skin incision, and (2) large bore cricothyrotomy cannulas and catheters. This differentiation is essential since narrow cannulas require high-pressure oxygen delivery for oxygenation and ventilation, while large bore cricothyrotomy cannulas and catheters enable regular (low-pressure) respiration and ventilation. Therefore, the availability of the ventilation system decides primarily the choice of the transtracheal equipment, but certain medical conditions also have an influence on the feasibility of the chosen material. If previously attempted oxygenation, ventilation and intubation techniques have failed, a nonsurgical oxygenation technique seems to be inappropriate, and there is no possibility to return soon to spontaneous ventilation, a surgical airway is urgently required. A surgical cricothyrotomy can be completed in less than 1 min of operating time when the anatomy is favorable. When no surgeon is available and as a last resort, this lifesaving intervention should be carried out without hesitation by any involved physician. Long-term oxygen therapy (LTOT) is an established treatment for endstage lung disease accompanied by hypoxemia. Oxygen delivery by nasal cannula is an uncomfortable mode of application for the patient and goes along with a decreased compliance. In contrast, transtracheal application of oxygen via a small catheter, which can be removed and cleaned by the patient over a minitracheostoma performed with local anesthesia on an outpatient basis circumvents these problems and enhances considerably the efficiency of LTOT.

One of the most concerning and potentially life-threatening challenges is unexpected difficulty in securing the airway and maintaining an adequate gas exchange. Although the term 'difficult intubation' is predominantly used in this context, the problem can encompass all facets of airway control, oxygenation and carbon dioxide elimination. The first and foremost concern has to be maintenance of adequate oxygenation. It should always have priority in comparison to intubation and even to ventilation. Next in importance is ventilation; this can be provided by expedient means, including face mask or laryngeal mask ventilation, and does not generally require tracheal intubation. The final consideration is to provide a secure, stable airway that can be used for an extended period. Alternative techniques for oxygenation and ventilation in the difficult airway have different degrees of availability, complexity and invasiveness. Simple techniques should be favored, whereas more invasive methods should be regarded as a backup to rely on when the initial technique has failed. However, when a 'cannot intubate – cannot ventilate' situation occurs, direct transcutaneous airway access is a rapid way to provide oxygenation. The cascade of options promoted by the American Society of Anesthesiologists includes standard and modified intubation attempts, mask ventilation, the use of numerous auxiliary devices such as laryngeal masks, the esophageal-tracheal combitube (a double-lumen device that is blindly introduced into the hypopharynx and is intended to allow tracheal ventilation via the lumen that matches the airway) and transtracheal oxygenation techniques [1]. The latter can be used, either to administer oxygen alone in order to prevent hypoxia or at least to achieve rapid reversal of hypoxemia, and under favorable circumstances to establish additional CO_2 elimination. In any case, oxygenation is the primary concern of these efforts. Usually, the establishment of a secure and patent airway has to be performed additionally after life threat has been overcome due to successful application of transtracheal oxygen.

Emergency Transtracheal Oxygenation Techniques

Anterior Cervical Anatomy

Knowledge of the cervical anatomy and especially of the predominant vascular pattern is of utmost importance. The same is true for the careful recognition of the transtracheal puncture site [2]. The distance from the skin surface to the airway lumen is mostly overestimated, but usually it is only about 5 mm. The anterior cervical region is well vascularized, but the cricothyroid membrane is nearly completely free of vessels and can be punctured without a high risk for bleeding, unless a clinically relevant coagulopathy is present. The nearest vessel is a small artery which follows horizontally the caudal edge of the thyroid cartilage. Therefore, the ideal place for the transcutaneous access to the airway is located right above the upper margin of the cricoid cartilage in midline position. This entrance to the airway also has the advantage of being the single place where a rigid dorsal wall which consists of the posterior part of the ring-shaped cricoid cartilage is present, and therefore protects the esophagus against inadvertent perforation. Nevertheless, in slim individuals, a more caudal puncture site is also possible, but one must be aware of the risks related to injury of the abundantly vascularized thyroid gland and the possibility of penetration through the posterior tracheal wall.

Performance of Transtracheal Puncture

Percutaneous puncture and catheter placement should be performed in a standardized fashion [3]. The patient must be positioned with the neck in maximal extension. The head retroflection can be facilitated by means of a folded cover placed under the shoulders of the patient. The benefit of this maneuver is an anterior displacement of the larynx effectuated by the cervical spine. Additionally, the skin will be more tightened and the puncture site can be recognized much easier. The larynx should be stabilized laterally by one hand, while the other performs the puncture. During tracheal penetration, the cannula must be kept perpendicular to the skin, and a characteristic loss of resistance will be noted when the airway is entered. Before advancing the catheter, it is essential to confirm intratracheal positioning by free aspiration of air. For this purpose, a 10-ml syringe should be used that can contain 2 ml of water in order to make air bubbles visible (fig. 1). At this point, the cannula tip is tilted caudally at an angle of 30° to the skin, and the catheter is advanced into the trachea while holding the introducer stationary. If a system based on the Seldinger® technique is used, the guidewire must be advanced before the catheter is moved forward. Following a second-position control by free air aspiration, the catheter is fixed to the skin and ventilation is begun. As with any delicate invasive procedure, there is a definite learning curve, and transtracheal puncture and catheter placement should not be attempted for the first time in an emergent situation. Practice can be obtained either in elective cases (maxillofacial or laryngeal surgery) or on the cadaver.

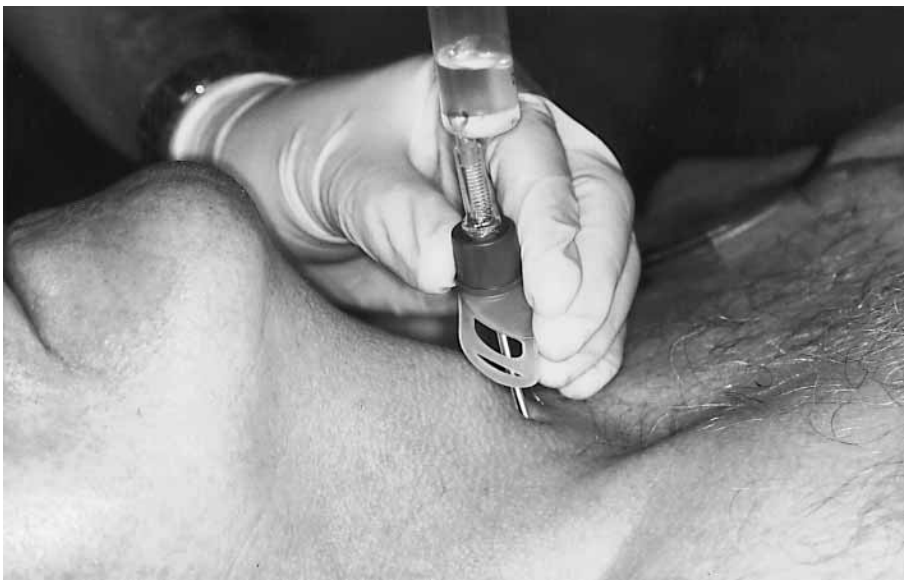

Fig. 1. Confirmation of intratracheal location of the cannula tip by air aspiration prior to advancement of the flexible catheter.

Transtracheal Equipment

From the technical point of view, two different categories of nonsurgical transtracheal equipment must be distinguished: (1) transtracheal puncture with narrow cannulas and catheters (ID usually <3 mm) and (2) cricothyrotomy performed with large bore cricothyrotomy cannulas and catheters. This differentiation is essential, since both techniques enable only the application of specific oxygenation/ventilation modes. Narrow cannulas require high-pressure oxygen delivery for oxygenation and ventilation. Low-pressure insufflation from the flush valve of an anesthesia machine can only prevent hypoxia, but even this limited achievement may be a valuable benefit, since it results in additional time for further airway management measures [4]. Squeezing a hand bag or ventilation via a circuit system usually fails to bring sufficient oxygen through narrow cannulas into the trachea. In contrast, large bore cannulas are designed for regular ventilation and should not be fitted to high-pressure oxygen sources or a jet ventilator. In order to prevent misunderstandings, commercially available equipment is designed according to the underlying methodological options: narrow catheters have a luer-lock connection that can be fitted with jet ventilation or insufflation devices, whereas large bore cricothyrotomy cannulas have a regular 15-mm connector for linkage with conventional ventilation systems. Unfortunately, some narrow cannulas are equipped with both connection types, and the 15-mm connector may mislead the user to try conventional ventilation, which in most cases may not be sufficient. It is essential to clarify in advance which kind of transtracheal equipment should be adopted in a specific location, whether it should be based on narrow or large bore cannulas and their respective oxygen delivery systems or whether a surgical cricothyrotomy should be preferred. Before the decision is made as to which system should be adopted, the specific advantages and disadvantages of all types of equipment should be considered (tables 1–3). However, the availability of equipment is not the only consideration in this context. Certain medical conditions of the involved patient also have an influence on the feasibility of these different transtracheal approaches. On an individual scale, there may also be arguments in favor of one or the other of the presented methods, and the appropriate choice can only be made accordingly if all kinds of techniques are available (table 4).

Oxygen Delivery Systems

Sufficient oxygenation can be provided by percutaneous transtracheal oxygen insufflation using narrow cannulas and low-pressure sources like the flush valve of an anesthesia machine. Though not allowing ventilation, this extremely simple and minimally invasive method can provide sufficient time to attempt alternative intubation techniques or create a more comfortable surgical airway [5, 6]. Since a sufficient carbon dioxide elimination cannot be achieved this way, this technique can only be adopted for a limited period of at least 15–20 min. Nei-

Table 1. Advantages and disadvantages of narrow transtracheal cannulas and catheters

Advantages	Disadvantages
Less invasive and less traumatic	Unsuitable for regular (low-pressure) ventilation
Simpler positioning and faster installation	Require additional exhalation outlet
Suitable for retrograde intubation (with rigid cannulas only)	Airway remains unprotected against aspiration
Suitable for insertion under local anesthesia	Higher risk of kinking, bending, distortion and obstruction of the catheter

Table 2. Advantages and disadvantages of large bore transtracheal cannulas and catheters

Advantages	Disadvantages
Suitable for regular (low-pressure) ventilation	More invasive
Do not require additional exhalation outlet	Cause more tissue damage
Offer a fair airway patency and protection	Insertion is more difficult, the installation is more complex

Table 3. Advantages and disadvantages of surgical cricothyrotomy

Advantages	Disadvantages
Offers best ventilation conditions	Is the most invasive method
Does not require additional exhalation outlet	Requires surgical instruments and certain surgical skill
Offers best airway patency and protection	Requires longest time period to be completed

Table 4. Arguments for decision making and choice of appropriate emergency transtracheal technique

	Narrow cannula	Large bore cannula	Surgical cricothy-rotomy
Difficult anatomical approach	++	–	+++
Only regular (low-pressure) oxygen source available	–	++	+++
Coagulopathy	++	–	+
Indication of awake application (under local anesthesia)	+++	–	+
Upper airway stenosis	–	++	+++
Shortage of time, imminent asphyxia	+++	++	–

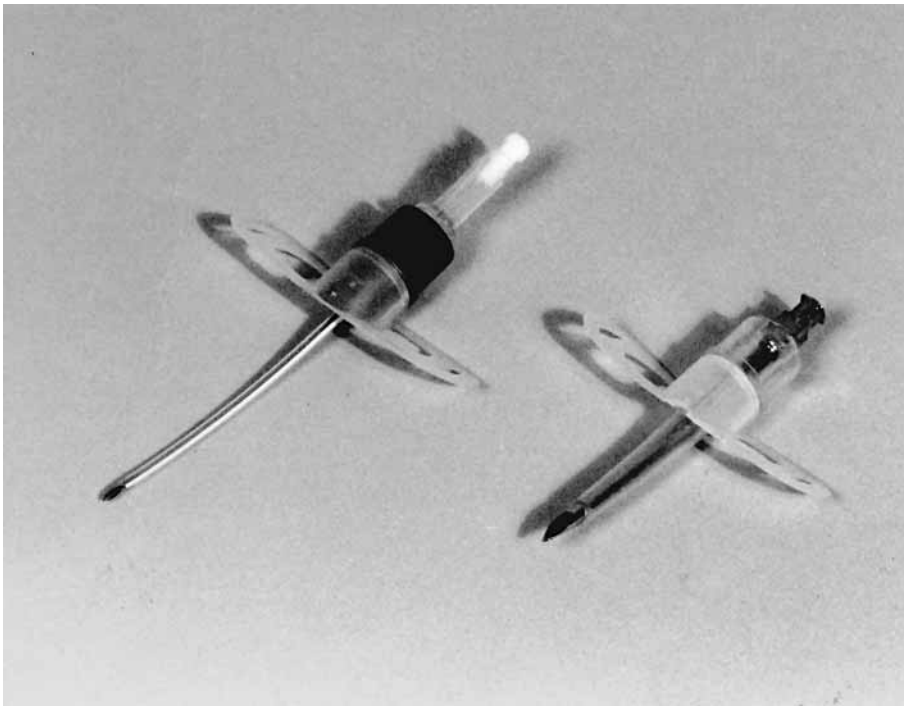

Fig. 2. A narrow Ravussin-type transtracheal cannula with catheter (left) for jet insufflation and a large bore Quicktrach cannula with catheter (right) for positive pressure ventilation.

ther the demand-valve device of an anesthesia machine, nor the bag-valve device can deliver the 1.5–4.0 atm required for adequate flow through such a narrow cannula. Only gas cylinders or a central source will be capable of generating sufficient oxygen pressure. A simple, low-cost hand-triggered jet injector is adequate. When the catheter is in place and connected to the injector, ventilation is begun at a rate of 15–20 cycles per minute. Oxygenation is monitored by pulse oxymetry. Effective ventilation occurs if thoracic excursion can be seen, and insufflation pressure should be adjusted according to the movement of the subclavicular region. Electronically operated jet ventilators have the advantage of on-line measurement of airway pressure with inbuilt automatic shut-down mechanism if a preset airway pressure limit is exceeded. To provide an egress for insufflated oxygen, it is important to ensure that the upper airway is at least partially open. This can be facilitated with an oro- or nasopharyngeal airway if necessary. For both transtracheal oxygen insufflation and jet ventilation, specially designed cannulas and catheters such as the Patil-set™, the Arndt-set™, and the Ravussin-type transtracheal catheter are available (fig. 2). To avoid potentially fatal complications, it is essential that the equipment is not assembled from random parts (intravenous catheters such as angiocath, syringe barrels, 3-way stopcocks, capnography tubing, standard 15-mm connectors). The contraindications include intrathoracic airway obstruction, inability to locate the cricothyroid membrane, severe pretracheal tissue distortion through which the cannula would be too short to penetrate and complete airway obstruction. The latter is essential, as any ventilation technique that depends on passive exhalation through an open outlet can increase intrathoracic pressure and may subsequently cause barotrauma [5].

Nonsurgical Cricothyrotomy

Percutaneous insertion of a large bore catheter is faster and less invasive than a formal surgical cricothyrotomy and does not require surgical instruments. On the other hand, this technique is somewhat more difficult and more invasive than transtracheal puncture with narrow cannulas. Several nonsurgical cricothyrotomy kits are commercially available, such as Quicktrach™, Nu-Trake™, Melker-set™ and Tracheoquick™, differing in shape, components and some details concerning the method of placement (fig. 2). They typically contain a sharp blade for initial skin incision, an introducer, guidewires, dilators and a large bore catheter with a standard 15-mm connector. These devices are favored when conventional ventilation with a bag-valve device is the only possibility available. The insertion technique is quite similar to the one adopted with narrow cannulas: positioning of the

head, neck and manual fixation of the larynx in the sagittal plane is the same as delineated above. A specific difference is the initial skin incision and the higher pressure that has to be applied for penetration of the involved tissues. Since the risk of tissue damage and related complications is probably higher than with narrow cannulas, regular practice of the technique on cadavers must be emphasized even more.

Surgical Access

When any alternative intubation method and even a nonsurgical oxygenation technique fails, and there is no possibility to return soon to spontaneous ventilation, a surgical airway is urgently required [7]. A surgical cricothyrotomy can be completed in less than 1 min of operating time when the anatomy is favorable. The procedure consists of making a horizontal incision directly through the skin and the cricothyroid membrane into the glottis. A flexible endotracheal tube (e.g. reinforced 5.0–6.5 mm ID) is then introduced into the trachea. In cases with gross distortion of the cervical anatomy, an emergent tracheotomy through a vertical incision may be required, though these situations should be anticipated a priori. When no surgeon is available and as a last resort, the involved physician should not hesitate to perform these procedures himself.

Long-Term Transtracheal Oxygen Therapy

Oxygen has been demonstrated to be the only drug to increase survival and also improve quality to life in patients with chronic obstructive pulmonary disease (COPD). The scientific evidence of this statement is based on two studies published two decades ago [8, 9].

The current indications for continuous long-term oxygen therapy (LTOT) are: (1) paO_2 less than or equal to 55 mm Hg; (2) paO_2 between 56 and 59 mm Hg if there is evidence of cor pulmonale, right heart failure or erythrocytosis (hematocrit >55%).

Oxygen may also be prescribed if (1) paO_2 is 55 mm Hg or less during sleep; (2) paO_2 drops to 55 mm Hg or less during exercise.

LTOT has not been documented to be effective in patients with COPD and milder degrees of hypoxemia [10]. However, this type of therapy may be of symptomatic benefit in patients with chronic hypoxemia due to other lung diseases besides COPD. Most patients receiving continuous domiciliary oxygen use oxygen concentrators with nasal cannulas. With this mode of application, oxygen is wasted to the atmosphere. Furthermore, some patients consider nasal cannulas uncomfortable or cosmetically annoying. These factors may adversely influence compliance.

Table 5. Potential benefits of TTOT

Eliminates irritation of the nose
Cosmetically more acceptable
Decreases O_2 requirement and enables greater mobility
Catheter does not fall off during the night
Enables adequate oxygenation in refractory hypoxemia
Enhances compliance

Advantages of Transtracheal Oxygen Delivery for the Patient

Transtracheal oxygen delivery avoids many of these problems (table 5). Oxygen is delivered through a catheter directly into the trachea, thus reducing wastage to the atmosphere and permitting a 50% reduction in oxygen flow rate for achieving the same degree of oxygenation. Portable cylinders of compressed oxygen or containers with fluid oxygen can be used for longer periods and higher arterial oxygen tensions can be reached with the flow-rates achieved by an oxygen concentrator.

The practicability of administering oxygen via a transtracheal system – transtracheal oxygen therapy (TTOT) – was demonstrated first in 1982 by Heimlich [11, 12]. Two types of transtracheal systems are most commonly used: (1) the Heimlich Micro Trach® system (Life Medical Technologies, Salt Lake City, Utah, USA); (2) the SCOOP® system (Transtracheal Systems, Denver, Colo., USA).

We use the SCOOP transtracheal system (fig. 3) and the procedure described by Christopher et al. [13, 14] and have personal experience with this technique with more than 100 patients [15, 16].

Procedure for the Transtracheal Insertion and Care

Transtracheal Procedure and Stent Week. The procedure is performed on an outpatient basis. The patient is seated in a chair with a headrest. Supplemental oxygen is delivered by cannula during the entire procedure. The notch of the thyroid cartilage, the cricothyroid membrane and the manubrium sterni are identified and marked with a surgical pen. The point of puncture of the cervical trachea is selected as the most convenient position for the catheter (fig. 4). The highest puncture is the cricothyroid membrane and the lowest the trachea at the level of the

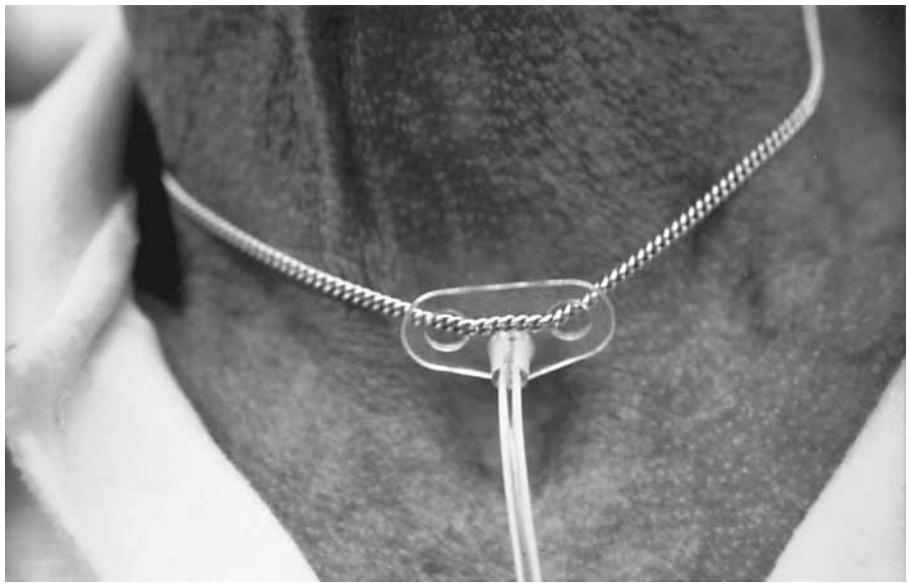

Fig. 3. SCOOP-II transtracheal catheter in place and secured with a necklace.

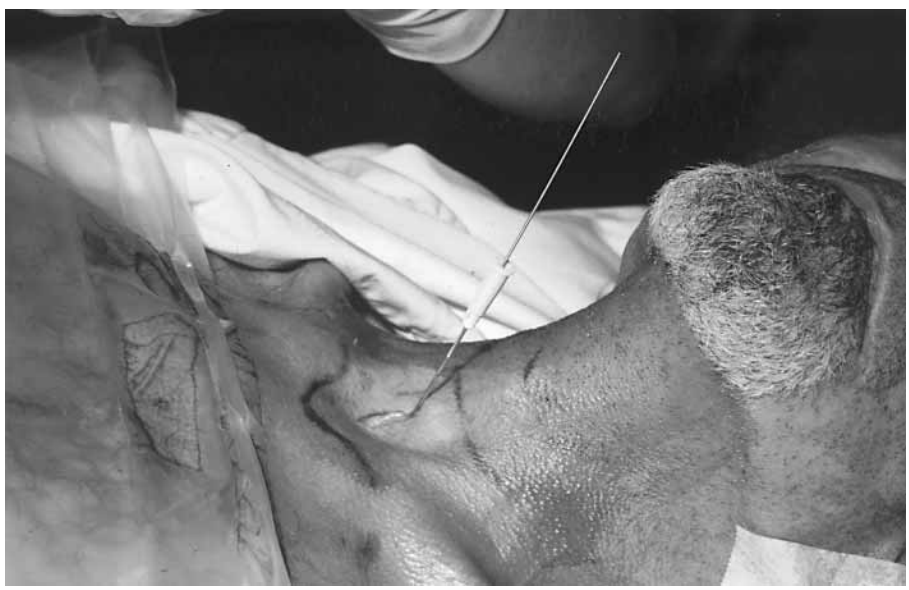

Fig. 4. Needle with guidewire between cricoid and first tracheal cartilage.

manubrium. Two percent lidocaine is injected into the dermis and the pretracheal soft tissue. Lidocaine is then injected transtracheally for endotracheal anesthesia. A scalpel is used to make a 1-cm vertical incision through the dermis at the puncture site. An 18-gauge thin-wall needle attached to a syringe containing saline is then directed through the incision into the trachea and air is freely aspirated. The syringe is then removed, the needle angled downward toward the carina, an atraumatic end of a wire guide is inserted through the needle into the trachea up to 11 cm. The needle is withdrawn, and a 10-french (1 french = 1/3 mm) dilator is advanced into the trachea over the wire guide. The dilator is exchanged for a 9-french tubular stent (Pre-SCOOP®; Transtracheal Systems), which is passed over the wire guide. The stent is then secured to the skin with two sutures. Codeine and an antibiotic are prescribed for 7 days.

TTOT over the Immature Tract. One week after the procedure, a guidewire is used to exchange the stent for a functioning transtracheal catheter. The catheter is a 9-french 20-cm-long reinforced tube with an internal length of 11 cm and one distal port (SCOOP-I®; Transtracheal

Systems). The catheter is secured around the neck with the bead chain necklace and then connected to the oxygen source by an oxygen hose with a security clip attached to the belt or other clothing to prevent inadvertent pull on the catheter. Transtracheal flow is titrated to obtain an arterial oxygen saturation higher than 90%. Patients are instructed to clean the catheter in place twice daily using 3 ml of normal saline or possibly 2% lidocaine and a cleaning rod.

During the cleaning procedure, patients often expectorate an accumulation of inspissated mucus which adheres to the catheter near the tip. If the mucus is not cleared, it can increase in amount until it partially or totally obstructs the trachea [17]. To minimize the risk of mucous ball formation, emphasis is placed on adequate humidification, frequent cleaning and early perception. The patient is instructed about symptoms which suggest mucous ball accumulation and he is told to call if he perceives any problem. Complications with mucous ball formation are commonest in this phase of the procedure, but may occur years after an uneventful transtracheal oxygen use. Patients with a very low peak flow and weak cough may be unable to dislodge the mucous ball by coughing. In this situation, removal of the mucous ball by fiberoptic bronchoscopy may be necessary.

TTOT over a Mature Tract. The patient returns 6–8 weeks after the initial procedure. The 9-french catheter is removed and an 8-french catheter with multiple side ports (SCOOP-II®; Transtracheal Systems) is inserted without the use of a guidewire. If any difficulty is encountered when the catheter is inserted, the tract is assumed not to be fully epithelialized, and the initial 9-french catheter is reinserted with the guidewire. The patient is told to use this catheter for an additional 2-week period before tract maturity is reevaluated. Once the tract is determined to be mature, patients are taught to remove, clean and reinsert the second catheter on a twice-daily basis. Patients who have problems to reinsert the catheter through the microstoma may be instructed to use a guidewire.

TTOT is an ideal method to deliver continuous oxygen in a highly motivated and compliant patient who has the strong desire to be active and mobile [18]. In other patients on LTOT, the insertion of a transtracheal catheter may be impossible or is contraindicated (table 6). TTOT is a method to be used by a team experienced with this type of procedure and well aware of and trained to handle potential complications (table 7).

Table 6. Contraindications for a transtracheal catheter

Absolute
Anatomic abnormality which makes insertion more difficult (severe obesity, goiter, deviated trachea, previous tracheostomy)
Severe coagulopathy
Production of copious amount of tenacious secretion (e.g. bronchiectases)
Risk of delayed healing (connective tissue disease, diabetes)
Lack of compliance
Relative
Inability for self-care

Table 7. Potential complications of a transtracheal catheter

Procedure related
Cephalad-displaced catheter
Subcutaneous emphysema
Early and usually transient complications
Increase in cough
Increase in sputum production
Expectoration of blood-tinged sputum
Minimal discomfort at the puncture site
Lost tract
Complications making removal of the catheter mandatory
Upper airway obstruction by mucous ball formation
Poor tolerance due to continuous irritation
Chondritis of a tracheal cartilage
Keloid formation

Oxygen Conservation

To obtain the same degree of oxygenation in a given patient only 50% of oxygen flow is required by transtracheal application as compared to the delivery by nasal cannula [14, 15]. This is advantageous for patients who can only be adequately oxygenated with high flows of oxygen (e.g. pulmonary fibrosis). Furthermore, it enables the patient to remain mobile and independent from his home base oxygen source for an extended period of time.

Potential Physiological Benefit of Transtracheal Oxygen Delivery

Besides the advantage of oxygen conservation, possible explanations for the added benefit of TTOT relate to the mode of administration more than the oxygen itself (table 8). Couser and Make [19] studied stable patients with different lung diseases while they breathed room air or transtracheally insufflated oxygen and found a decrease in

Table 8. Physiological benefit of transtracheal oxygen therapy

Decrease in dead space	O_2 is delivered by the catheter directly into the bypassing upper airways and decreasing dead space
Increase in CO_2 elimination efficiency	CO_2 flushes outward from the upper airways during exhalation of the oxygen flow
Decrease in work of breathing	

inspired minute ventilation measured at the mouth without changes in blood gas tension. Another group found a drop in patient-generated minute ventilation and no change in $paCO_2$, which is best explained by a decrease in dead space [20, 21]. Benditt et al. [22] found that transtracheal delivery of oxygen or air reduces the oxygen cost of breathing as estimated by calculation of the pleural pressure-time index. TTOT was associated with a less demanding respiratory pattern of breathing for the diaphragm.

These findings help to explain the improvements in exercise tolerance and decrease of dyspnea that are noted clinically. Another elegant study showed in a randomized, double-blinded manner that patients with COPD have a greater exercise tolerance when using TTOT than when using nasal cannula delivery [23]. It was found that the improvement is not related to improved arterial oxygenation.

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Interventional Bronchoscopy beyond the Year 2000

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Autofluorescence Bronchoscopy: The Laser Imaging Fluorescence Endoscope

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Summary

In conventional bronchoscopy, detection and localization of dysplasia and carcinoma in situ (CIS) has been limited to roughly 30% of the total number thought to be present. Using a special light source which generates monochromal light of 442 μm and a digitalized integrated two-camera system 30,000 times more powerful than usual endoscopic cameras, the Laser Imaging Fluorescence Endoscope (LIFE®) system is said to be able to detect these lesions more readily. In our initial results from 144 bronchoscopies with 253 biopsies, in which a total of 50 severe dysplasias and/or CIS were cyto-histologically confirmed, 39 (78%) were correctly identified by the combined white light + LIFE modes, while only 15 (30%) were noted on white light alone. These results are largely in agreement with other international studies also reviewed in this chapter. The complication rate of the combined procedure is not higher than for conventional bronchoscopy alone, the intervention is performed under topical anesthesia as an outpatient procedure, and the examination time is increased by approximately 10 min only, compared to conventional flexible bronchoscopy. Improved ability to diagnose pre-neoplasias and early lung cancer lesions will not only result in more lives being saved, but will also provide whole new insights into carcinogenesis, with promising ramifications for yet further improvement in diagnosis and therapy of lung cancer.

Assessment of earlier chest X-ray screening studies [1] and recent technological innovations have reawakened interest in early – or asymptomatic – lung cancer (ELC) diagnosis. Whereas X-ray may be helpful for peripheral lesions, for centrally located, radio-occult and exfoliative tumors – usually squamous cell – sputum studies can be useful [2]. Once suspicious cells have been detected, sensitive endoscopic procedures can be used to localize discrete, early lesions, most of which are curable [3]. More than 80% of X-ray-occult cancers are located in the visible portion of the tracheo-bronchial tree [4], and, once localized, at least 80% can be cured, either through surgical resection or, in cases of functional inoperability, through interventional procedures [5, 6]. In spite of most ELCs being situated within the visible range of endoscopes, their precise localization has been disappointing. This paradox is due primarily to the predominant intraepithelial growth pattern of most ELCs, which is difficult to visualize, as compared to the easier-to-spot, yet more seldom, polypoid tumor. The intraepithelial pattern shows only very discrete spur thickening and mucosal irregularity, minor vessel dilatation, localized edema and distorted light reflex, all of which are particularly difficult to recognize in the presence of chronic bronchitis. Even notable improvement in fiber- and video-optic technology of modern, conventional endoscopes has not significantly improved diagnosis here [7]. Systematic segmental wash-

ings for ELC localization are time-consuming and cumbersome for the bronchology unit, and patient compliance for repeated follow-up is low; Saito et al. [8], for example, reported a 25% dropout rate. The localization of ELC can, however, be significantly improved with the autofluorescence bronchoscope, or the Laser Imaging Fluorescence Endoscope LIFE® system, described below.

Materials and Methods

'Fluorescence' is a physical phenomenon, a form of luminescence or 'cold' light emission. It occurs when an object on which light of a certain wave length is directed remits light of a longer wave length. Its effect on body tissue has been recognized since the early 1900s ('Wood's light', [9]. In 1943, Herley [10] described fluorescence tissue reaction to ultraviolet light, noting even then that a tumor behaved differently than healthy tissue. Substances responsible for fluorescence, fluorophores, yield organ-typical patterns, are variously concentrated within organs and may change according to prevailing conditions. The many fluorophore subtypes include tryptophane, collagen, elastine and porphyrine; participating in the oxidative metabolism NAD/NADH pyridoxal phosphate and flavines [11]. Wave length and intensity of fluorophore-emitted light depends on their concentration, their maximal absorption and remission, and, of course, on the characteristics of the exogenous light source.

Compared to light visible to the unaided eye, autofluorescence of bronchial mucosa is extremely weak and cannot be visualized unless strongly amplified, an effect also caused by porphyrines, which selectively concentrate in malignant tissue. Efforts at using hematoporphyrine derivatives (HpD) [12] as a diagnostic aid have, however, proven unsuccessful for a variety of reasons, including costs, complications, and poor specificity. While attempting to reduce the amount of HpD to an absolute minimum, Staël v. Holstein et al. [13] and Lam et al. [14] discovered that even in complete absence of HpD, tumorous tissue could be distinguished from normal by a noticeable reduction of autofluorescence – the key step to LIFE bronchoscopy!

When monochromal light of 442 µm is directed at mucosa, subepithelial fluorophores are stimulated to emit light of a longer wave length. This emission is a mixed signal, consisting of a stronger green peak of 520 µm and a weaker red one of 630 µm wave length. The digitalized image on the video screen is green. In carcinoma in situ (CIS) or dysplasia, both the intensity of emitted light is weaker (approximately ten times in CIS) and the light composition is altered in favor of the red spectrum (fig. 1–4). Reduced fluorescence is due to epithelial thickening, tumor hyperemia (hemoglobin absorbs virtually all the green light), redox changes in the tumor matrix and reduced fluorophore concentration [15]. It has been possible to integrate the millions of emitted fluorescence signals through digital technology, thus producing a real-time video image of bronchial mucosa, through the autofluorescence bronchoscope, the LIFE system (Olympus/Xillix) [16]. The light source, a low-intensity helium-cadmium laser, generates the 442-µm monochromal beam, which is conducted to the mucosa via a conventional bronchoscope (Olympus BF-20 or BF-40]. The red and green emissions are registered, respectively, by two integrated, high-resolution charge-coupled device cameras and the digitalized impulses conducted to a mother board, which processes them into the real-time video image for the endoscopist (fig. 2). The monitor image of normal mucosa appears light green; dysplasia and CIS or tumor reddish-brown. Normally, a conventional white light bronchoscopy (WLB) with usual inspection preceeds the LIFE examination. Photosensitizers are not required, and the bronchoscope remains intubated when switching from one system to another.

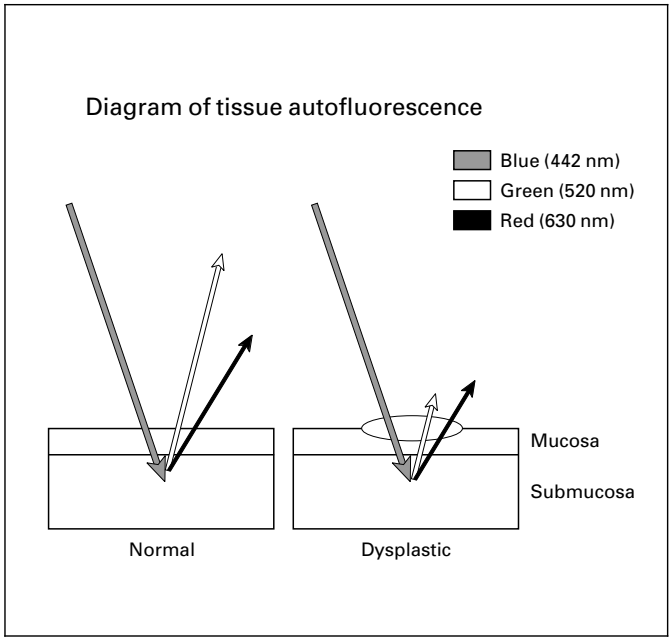

Fig. 1. Fluorescence light-emitting characteristics of normal bronchial mucosa and bronchial mucosa altered by dysplasia and CIS.

The LIFE examination is done under topical anesthesia; optimal premedication is essential to minimize cough and restlessness. The combined WLB and LIFE endoscopy result in increased examination time from 5–15 min compared to conventional procedures alone. Suspicious findings are documented and classified in both LIFE and WLB modes, and biopsies may be taken in either.

Certain points should be considered in assessing diagnosis of early lung cancer with the LIFE system. The limited optical spectrum on which the video image is based narrows, of necessity, the breadth of visual information. Secretions, hyperemia, inflammation or spacial orientation may well be better assessable by WLB. Hence, optimal results can be expected only by combining the procedures. It follows that even in assessing the diagnostic rate for early lung cancer, the most logical comparison is WLB alone, compared to WLB + LIFE combined. The concept of 'sensitivity' needs also to be redefined in this context, since only individual biopsies of a lesion are taken with a few control biopsies, and to biopsy all normal sites is impossible. So 'relative sensitivity' is the term used, meaning the number of correct positive biopsies in WLB compared to those with the combined – WLB + LIFE – procedure.

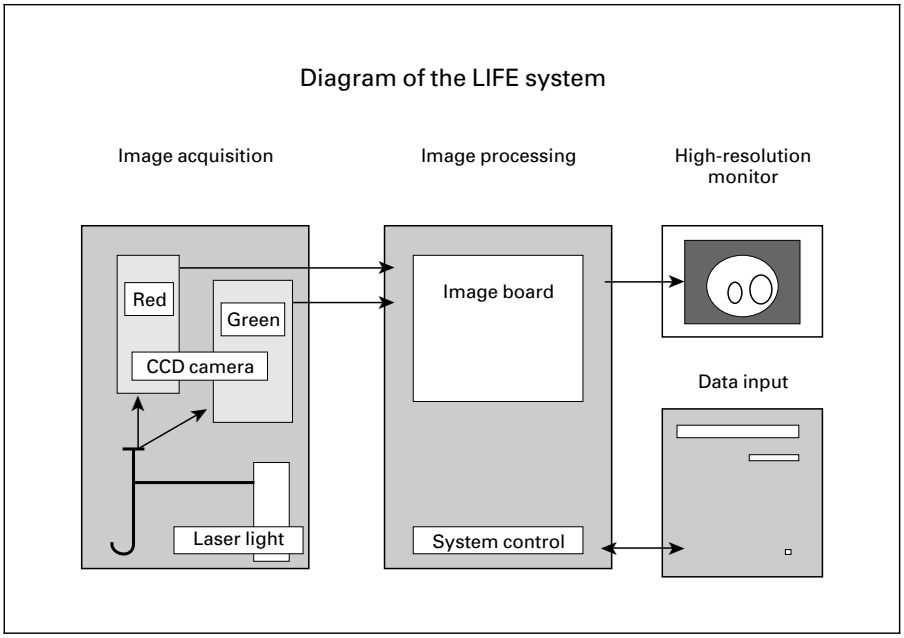

Fig. 2. Diagram of the LIFE (Olympus/Xillix) system. The key elements are the digitalized, powerful, integrated two-camera system and the monochromal-light-generating helium-cadmiun laser.

Results in the Diagnosis of Dysplasia and CIS with the LIFE System

International Publications

In 1992, Lam et al. [17] performed autofluorescence bronchoscopy in 82 asbestos- and/or diesel-exposed volunteers. Their results showed a sensitivity for moderate to severe dysplasia and CIS of 52% for WLB and 86% for LIFE, with corresponding specificities of 81 and 79%. A total of 238 biopsies were taken, resulting in 12 moderate and 6 severe dysplasias, and 3 CIS.

In 1994, in a prospective study of patients with suspected lung cancer or in postresection follow-ups, which also included volunteer smokers (>25 pack years) as controls, Lam et al. [18] reported an increase in CIS diagnosis with LIFE to 91% from 40% with WLB (35 lesions). The diagnostic rate in 78 dysplasias increased from 38.5% for WLB to 78.1% for LIFE. The authors reported only a minor loss in specificity for LIFE (86.7%) compared to WLB (91%).

In 1998, the results of a North American multicenter study in 173 patients with suspected lung cancer, in whom WLB was followed by the fluorescence mode [19], were as follows: from a total of 700 biopsies, 142 were moderate to severe dysplasia, CIS or invasive cancer. Whereas 35 of these lesions were recognized by WLB, 91 were correctly identified in the LIFE mode, corresponding to a relative sensitivity of 2.71 [19].If only intraepithelial lesions were considered, the relative sensitivity increased to 6.1 for the LIFE mode. There was, however, a fourfold increase in the rate of false positives for the LIFE system. Results of the European Multi-Center Study on Diagnosis of Early Lung Cancer with the LIFE System, still to be published, are in broad agreement with those reported above.

Table 1. Indications for LIFE bronchoscopy

Indications	Examinations
Radiological changes suggestive of lung cancer	67
Follow-up after resection for cure	61
New respiratory symptoms in patients at risk	41
Positive sputum cytology or previous dysplasia	28
Upper aerodigestive tumors, staging	14
Others (smokers, industrially exposed)	32
Total	243

Reporting on both precancerous and obviously manifest tumors in 1997, Yokomize et al. [20] found a WLB diagnostic rate of 63%, and of 89.5% with WLB + LIFE. The total number of lesions was, however, only 14, and included only a few preneoplasias [20].

Authors' Results

Autofluorescence bronchoscopy with the LIFE system has been in routine use in the Bronchology Unit of the

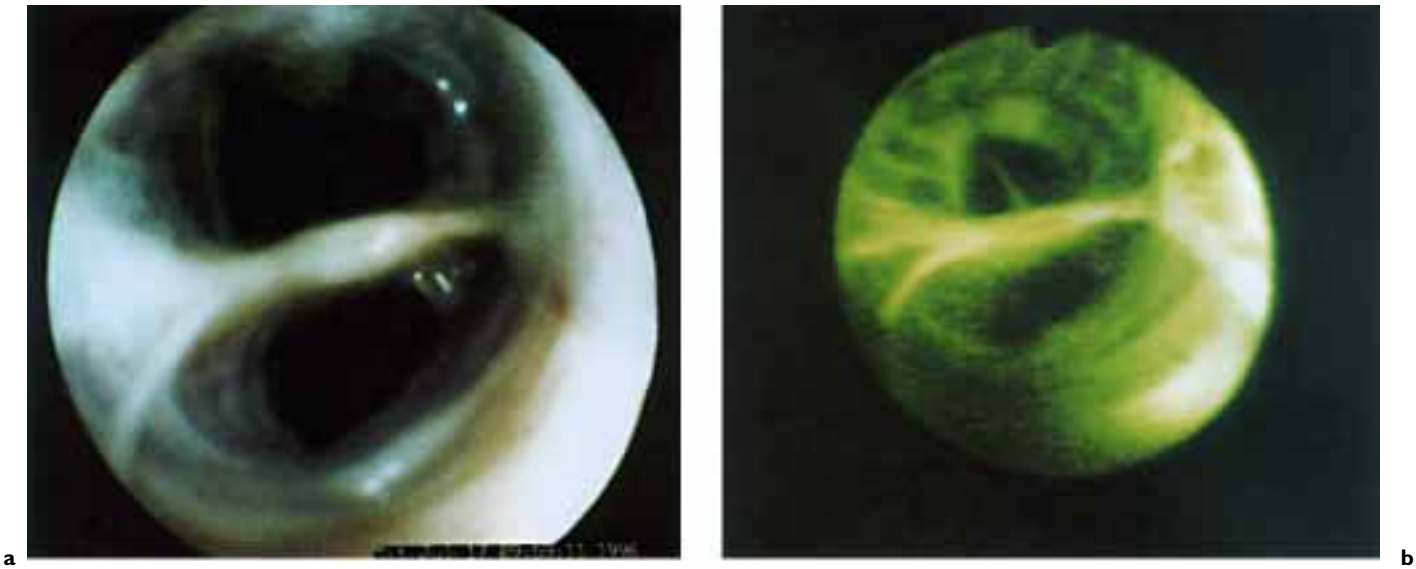

Fig. 3. a A slightly thickened subsegmental spur looking otherwise normal in the conventional, white light mode. **b** The same spur seen in the LIFE mode: no reduction in fluorescence characteristics, normal finding.

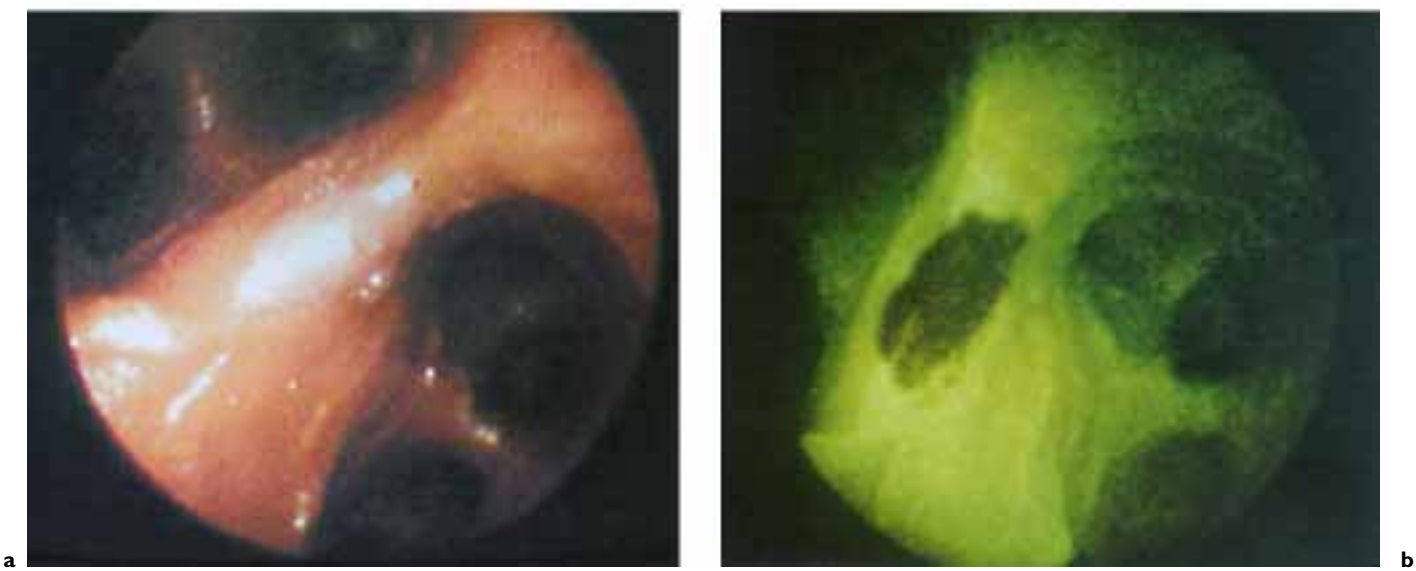

Fig. 4. a Segmental RB 9/10 spur in white light mode: slightly thickened, but no suspicious mucosal changes. **b** The same subcarina in LIFE mode: sharply delineated, oval region at medial orifice of RB 10 with significantly reduced fluorescence: macroscopic DD: severe dysplasia, CIS.

Pulmonary Department, Augusta Teaching Hospital, since May, 1995. Data, analyzed from the first 2 years, show 244 combined WLB + LIFE examinations on 201 patients (39 females), with more than one examination usually as postresection follow-up (table 1). All suspicious findings were video- and photo-documented, anatomically designated and classified as normal or inflammation (Class I), suspected dysplasia or CIS (Class II) or manifest tumor (Class III). In 144 bronchoscopies, a total of 253 biopsies were taken; these included random biopsies of

Table 2. Diagnostic Rate of LIFE compared to WLB

Endoscopic diagnosis		Tissue diagnosis	
WLB	LIFE	(pre-)neoplasia	no (pre-)neoplasia
Suspicious	Suspicious	15	24
Nonsuspicious	Suspicious	24	59
Suspicious	Nonsuspicious	0	8
Nonsuspicious	Nonsuspicious	11	86

Total: endoscopic diagnosis n = 227; (pre-)neoplasia n = 50; no (pre-)neoplasia n = 177.

normal-appearing mucosa for a multi-center study. Only 5 biopsies were considered inadequate for histology, and 22 were excluded due to previous biopsy at the same site. Metaplasia and mild dysplasia were classified as normal (Class I), moderate to severe dysplasia and CIS as abnormal (Class II). Excluding manifest tumor (Class III), a comparison was made between the suspected endoscopic diagnosis and cyto- and/or histological final diagnosis in 227 biopsies (table 2). From a total of 50 moderate to severe dysplasia or CIS, 39 (78%) had been identified by WLB + LIFE, whereas only 15 (30%) were noted by WLB, corresponding to a relative sensitivity of 2.6 for the combined procedure. From 97 random (control) biopsies, histology confirmed normal findings in 86. In 11 controls, however, varying degrees of dysplasia, and even one CIS (cytology), were found. Eight examinations (3.7%) were aborted due to excessive cough, a figure corresponding to that in conventional bronchoscopy. Side-effects due to stronger sedation, increased examination time, or more biopsies were not observed.

In our unit, the addition of autofluorescence bronchoscopy with the LIFE system to conventional bronchoscopy, has resulted in an improved relative sensitivity of 2.6 for the diagnosis of dysplasia and CIS.

Discussion

Recent experience shows that the addition of autofluorescence bronchoscopy to conventional endoscopy can significantly improve the endoscopic diagnosis of preneoplastic lesions and early lung cancer. Improved diagnosis is thus obtained without need of tumor sensitizers and with complication rates comparable to conventional bronchoscopy. Relatively low specificity (i.e. too many false positives) remains a problem; however, in both LIFE and WLB, inflammatory or granulomatous pathologies, or any number of other localized changes, may mistakenly be taken for early or preneoplastic lesions. The problem is not unique to fluorescence endoscopy, but it deserves further attention in both modes.

The degree of fluorescence loss correlates with the gradual change from metaplasia to mild, then to moderate and severe dysplasia, and, ultimately, to CIS [21]. With increasing experience, the endoscopist can learn to differentiate these gradations macroscopically, to some extent. Experience also helps recognition of artifactual (traumatic), inflammatory and granulomatous alterations. In training for LIFE bronchoscopy, 25 examinations in a teaching setting are generally recommended before the endoscopist goes 'on his own'. And for the teaching unit, the Broncho-Boy Universal Teaching Model (CLA, Coburg, Germany) has been further modified to include the fluorescence tracheobronchial tree, which looks normal in white light, and light green on LIFE bronchoscopy, with areas of reduced fluorescence not visible in the white light mode.

One unanswered question is whether metaplasia and mild dysplasia are, of necessity, a part of progressive development from preneoplasia to neoplasia, or whether these are simply spontaneously reversible, reactive changes [25]. CIS is, by definition, irreversible, but what about severe dysplasia? Besides, genetic instability (which may lead to cancer) has been demonstrated in morphologically quite normal-looking mucosa [22–24]. The problem is further confounded by the fact that about 10% of dysplasias and CIS do not even cause thickening of the epithelium [le Riche, pers. commun, January, 1999]. Since epithelial thickening is considered one of the main causes of reduced fluorescence, will individual lesions in this 10% group even show up on fluorescence? These are open questions in the spring of 1999, but for the LIFE bronchoscopist, they do emphasize the importance of taking as

many random biopsies as possible (6 is a good number to aim for).

Several benign mucosal changes can mislead the examiner: granulation tissue, rich in capillaries with a high content of hemoglobin, absorb fluorescence light, as do mucosal traumata. Some patients tend to respond to biopsy by a reactive hyperplasia (i.e. reduced fluorescence), a phenomenon observed on follow-up LIFE examinations. Tangential light may cause shadowing which can only be resolved by increasing the angle of the tip of the scope to the mucosal plane to as close as possible to 90°.

Growth patterns of early cancers amenable to LIFE diagnosis are superficial. Maximum penetration of the laser light is to the submucosal level [15], hence early tumors developing from deeper layers, e.g. small cell cancer, are undetectable by the LIFE mode.

Both in our series and in other published studies, a number of cytohistological positive precancerous and CIS lesions have been found in endoscopically 'normal' random biopsies. A partial explanation of these false negatives may be the 10% of dysplasias and CIS which do not cause thickening of the epithelium (see above).

Current interest in diagnosis of ELC has spurred a number of alternative fluorescence techniques which have yet to be validated on a larger scale. These include the 'optical multichannel analyzer', which, combined with photosensitizer, has been reported to diagnose 12 relapses in 'for cure' resected patients [26]. Consisting of a single beam which is swept over the area of interest, this method requires prior identification and delineation of the area of interest through conventional endoscopy. The system is being further expanded and developed [27]. Other systems (Pentax, Storz) are being clinically tested in studies which include fluorescence detection of manifest tumors – i.e. those readily seen in white light – in their analyses, as has been done previously [20]. Since fluorescence systems are designed to detect changes occult to white light, it would seem irrelevant to use these for manifest tumors – unless these studies are designed to broaden the statistical base for analyzing results, which some may consider a reasonable point (the authors do not).

In the patients reported here, precancerous lesions occurred often as a second finding in known lung cancer, an observation, also made by others, which indicates that up to 15% simultaneous lesions may exist [28]. Hence, it is reasonable to integrate LIFE bronchoscopy in preoperative staging. Follow-up bronchoscopy in 'for cure' resected lung cancers should also include fluorescence bronchoscopy for the same reason [29]. Staging for upper aerodigestive tumors is a further indication [30].

Industrially exposed workers may be another group to profit from autofluorescence bronchoscopy, as the study referred to above by Lam et al. [17] indicated. But for obvious reasons, as a screening procedure, sputum studies should preceed any endoscopic measures. By the same token, heavy smokers should also submit themselves to sputum screening studies, since modern automated cytometry [31–33] shows promise in narrowing down the number of patients requiring endoscopy. Many of the patients referred to us for LIFE bronchoscopy have previously had suspicious cytometry findings.

Improved localization of dysplasias with the LIFE system can be used together with studies on chemoprevention [34] and tumor genesis. Also, fluorescence changes of tumor-adjacent tissue may yield important information regarding the body's tumor defenses. The next phase of development of fluorescence bronchoscopy will include cheaper and less cumbersome systems becoming affordable for an increasingly growing group of endoscopists and researchers.

Conclusion

In multicenter trials and in the authors' experience, autofluorescence bronchoscopy, or the LIFE system, has been shown to increase diagnosis of dysplasia and CIS when used in combination with conventional bronchoscopy; it is, as such, a significant advance in ELC diagnosis. Thanks to the wide spectrum of interventional procedures for endoluminal treatment of lung cancer in functionally inoperable patients, even this group can profit from LIFE bronchoscopy. Submucosal tumors or those with a very high replication rate are less amenable to LIFE diagnosis. Notwithstanding this limitation, the doubling to tripling of the rate of early centrally located lung cancer diagnosis does provide a significant window of hope for patients afflicted with lung cancer. The LIFE system provides this window without the need for exogenous sensitizers, no increase in complications compared to conventional bronchoscopy and little increase in examination time.

Note Added in Proof

Since this chapter was written, the research and development collaboration between Olympus Optical Co. and Xillix Technologies has been terminated. Olympus remains, however, fully committed to further development of diagnosis and treatment modalities for early cancers. *-JAN*

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Autofluorescence Bronchoscopy: The D-Light System

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Summary

Early malignant changes are difficult to detect by conventional white light bronchoscopy (WLB). These lesions are only a few cell layers thick and some millimeters in surface diameter. Therefore, the endoscopic changes are very subtle and can be missed even by experienced bronchoscopists. On the other hand, dysplasia and carcinoma in situ occur in up to 10% of high risk patients. New methods can help to improve the detection rate of these findings. The most promising technique for this purpose is based on the detection of autofluorescence phenomena. Up to now, several different systems have been developed, some of them being in the state of clinical evaluation. All fluorescence bronchoscopy systems depend on the individual, subjective experience of the investigator. The technical and scientific effort aims firstly to simplify the technical procedure, secondly to objectify the endoscopic findings, and thirdly to increase sensitivity and specificity further on. Some possibilities to obtain these targets are: (1) Replacement of lasers by conventional white light sources with the advantage of using WLB and autofluorescence bronchoscopy (AFB) in one diagnostic procedure. (2) Development of appropriate image processing routines and implementation of wavelength-resolving spectral analysis. (3) Integration of various filters for emission of specific wavelength is necessary to stimulate exogenous fluorescence sensitizers (e.g. aminolevulinic acid). (4) Combination of various detection methods in one technical system. Some of the above-mentioned targets have been implemented in a newly developed diagnostic system described in detail in this paper. Preliminary results of this system show a more than twofold increase of the sensitivity for early stages by the use of additional AFB in comparison to WLB. Future research should be focused on the use of autofluorescence phenomena on a cellular level too. The diagnosis of early malignancy should include newly developed cytological methods to preselect patients with clinically occult malignancies within a screening program. Finally, these highly selected patients should be investigated by highly efficient interventional fluorescence bronchoscopy methods to localize and to characterize the malignancy. This will offer the chance for endoscopic therapeutic procedures and might help to significantly reduce mortality for patients with lung cancer.

Early diagnosis and localization of lung cancer is an essential precondition for its curative treatment [1, 2]. Detection of early lung cancer may be helpful for two reasons: Firstly, carcinogenesis is a slow process evolving over years and is estimated to take 3–4 years for dysplasia and approximately a further 6 months for carcinoma in situ (CIS) [3, 4]. Secondly, about 50–60% of all lung cancers, especially squamous cell carcinomas, develop in the central airways [5]. This means that we have a window of

time for early detection, and most of the lesions in the central airways are accessible with the flexible bronchoscope [5]. On the other hand, there is a high prevalence of synchronous early carcinomas and metachronous carcinomas in patients at risk. Based on an investigation of section specimens of complete lungs, Auerbach et al. [6] found a prevalence of carcinoma in situ in 4.3 and 11.4% of slight and heavy smokers, respectively. Fifteen percent of all patients dying from bronchial carcinoma had synchronous carcinomas in situ. In patients with radiologically occult lung cancer, carcinoma in situ was found in 20% and microinvasive carcinomas were found in 41% [7]. These factors offer a chance for screening to detect early malignancies in high-risk groups for curative endoscopic therapy. The lesions, however, are usually small and only a few cell layers thick [8]. Sensitivity and specificity of conventional bronchoscopy for detection of pre- and early malignant changes therefore are low [9]. Subtle changes indicating these findings can be missed easily even by experienced endoscopists [10]. On the other hand, these subtle changes can be mimicked by inflammation. This was shown in a study by Sato et al. [11], where only 14% of the bronchial biopsy specimens taken from abnormal areas of the bronchial mucosa were confirmed as moderate to severe dysplasia or cancer.

To improve sensitivity and specificity, diagnostic fluorescence procedures have been developed since the early 1980s [12]. The principles of these procedures are based on a difference in fluorescence between normal tissue and malignant tissue [13] and have been discussed in the chapter on autofluorescence bronchoscopy by Nakhosteen.

Two basic methods are available to make this difference visible: (1) the detection of the specific autofluorescence of tumor tissue and normal tissue [14]; (2) the application of photosensitive drugs, which selectively accumulate in tumor tissue and cause a specific drug-induced fluorescence [15]. Up to now, different technical features based on these methods have been developed in Canada [16], Japan [17] and Germany [18–20], some of them are in clinical evaluation.

History of Autofluorescence- and Drug-Induced Fluorescence Bronchoscopy

Fluorescence bronchoscopy has been developed over the last two decades, yet the process of technical improvement and clinical evaluation is still going on. Pioneering observations focusing onto the phenomenon of distinct autofluorescent characteristics of normal tissue and tumor tissue were reported by Sutro and Burmann [13] in 1933. In the 1960s, Lipson et al. [21] described the preferential retention of hematoporphyrin derivatives by tumor and the tumor-localizing properties of this substance. Fluorescence bronchoscopy was developed in the early 80s mainly using fluorescing drugs [22] and later on based on autofluorescence [23]. Drug-induced fluorescence is characterized by emission of red fluorescent light when excited by violet light. The main limitation of porphyrin-based fluorescence, however, is caused by its cutaneous photosensitivity [24]. The low-dose photofrin 2-wavelength method which was tested to avoid this side effect in the early 90s could not be established clinically [15]. Hematoporphyrin derivatives have recently been replaced by 5-aminolevulinic acid (ALA; Medac Company, Hamburg, Germany) [25]. Presently ALA-induced fluorescence is a field of hopeful investigation and may be an option for clinical use in the future [26, 27].

Another approach has been made by Hung et al. [14] based on the observation of reduced autofluorescence intensity in tumor lesions compared with normal tissue. After several steps of technical developments, finally the Lung Imaging Fluorescence Endoscopy (LIFE) was developed by the British Columbia Cancer Agency in collaboration with Xillix Technologies Corporation in Vancouver. It is comprised of a helium-cadmium laser light source, two image-intensifier CCD cameras and a color video monitor [16]. The system has been evaluated clinically by two large multicenter studies [28, 29]. It has been demonstrated to have significant clinical benefit in early detection of dysplasia and CIS. However, the system is technically complex, its handling is uncomfortable and does not allow direct and immediate comparison of white light and autofluorescence imaging, and last but not least its costs are high.

To avoid these disadvantages, currently some new technical features have been developed. In the following, we will describe the detection of the specific autofluorescence by stimulating the tissue with an incoherent light source, developed by Storz company (Tuttlingen, Germany) in collaboration with the Laser Forschungs Labor of the University of Munich, Germany [19]. This system is a modification of the ALA-based method primarily used in urology [30].

Before discussing the components of this system, some principles concerning the underlying biophysical principles have to be outlined.

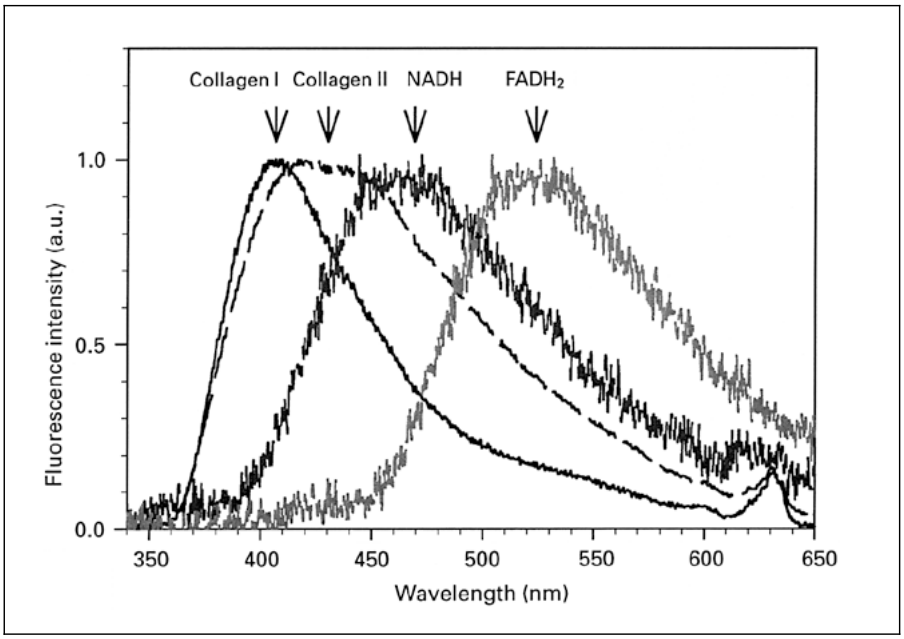

Fig. 1. Emission spectra of different chromophores of the tissue after excitation with light from a XeCl laser (308 nm). NADH = Reduced nicotinamide adenine dinucleotide; $FADH_2$ = reduced flavin adenine dinucleotide.

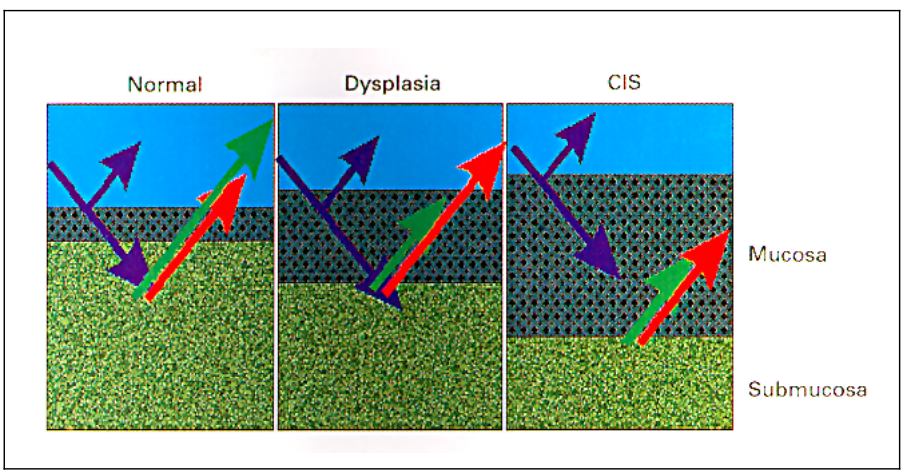

Fig. 2. Effect of the thickened epithelium of pre- and early malignant tumors (for example dysplasia, CIS) on excitation light (blue) and the fluorescent light (red, green) emitted from the submucosa. A low part of the blue remission light (blue reflected arrow) is used for enhancement of the contrast.

Biophysical Principles of Autofluorescence Light – Basis for a Newly Developed System

To evoke autofluorescence, an excitation light source in the near ultraviolet range up to blue light (250–500 nm) is required. Various chromophores embedded in cells and tissue structures are known to emit fluorescence [31]. The excitation and fluorescence spectra of the dyes involved typically show broad band widths. Figure 1 displays several molecules which are expected to play an important role in autofluorescence when excited with a XeCl laser at 308 nm [32].

Incoherent light (380–460 nm) has an adequate effect for the emission of the above-mentioned fluorophores, but since blood absorption is lower in the range of excitation and emission, the light penetrates deeper into the tissue and excites green to red fluorescence originating mainly from the submucosa. This fluorescence, however, is very weak; not more than 1% of the excitation light is transformed to fluorescence light [33]. On the other hand, about 40% of the blue excitation light is remitted from the surface of the tissue and covers the weak fluorescence light originating from the submucosa [34]. To make autofluorescence light visible for clinical use, these problems

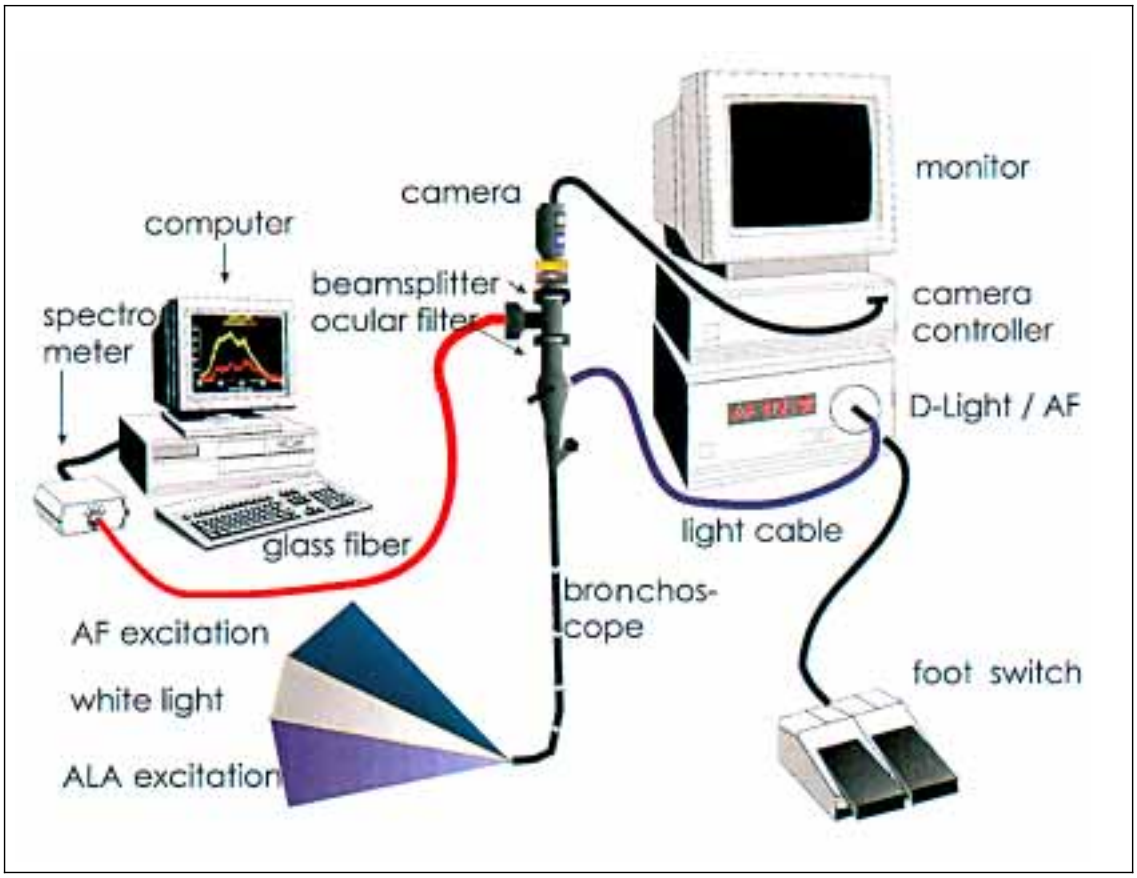

Fig. 3. Technical setup. AF = Autofluorescence.

are solved by two basic technical developments: Firstly, excitation is caused by a high-power light source, and transmission is realized with minimal loss of light intensity by a liquid light guidance. Secondly, most of the reflected blue excitation light is eliminated to achieve visibility of the fluorescence light [35].

In contrast to other autofluorescence systems, the newly developed system does not block off the blue excitation light entirely. So the blue component originating from the scattering of the upper layer of the tissue increases the overall light intensity [36]. Additionally, the blue component is used as a reference to generate a color contrast for discriminating tumor tissue from normal tissue [37].

An explanation for the contrast between tumor and normal tissue may be a higher absorption of light by the thickened epithelium and/or a reduced fluorescence excitation of chromophores in the submucosa due to the limited penetration depth of the blue excitation light (fig. 2) [38]. Finally, the concentration of the fluorophores in tumor tissue may be reduced in comparison to normal tissue. The blue remission and the red fluorescence light are not reduced by the same amount as the green fluorescence light [39]. As a result, the color of malignant areas appears bluish-reddish and darkened. In contrast, the color of the normal mucosa is dominated by the green fluorescence component [40]. Endoscopically, malignant tissues are indicated by specific changes in color and disturbance of relief and fine structure of the mucosal surface.

Autofluorescence Detection with the Newly Developed System D-Light/AF

Technical Components

The D-Light/AF system offers three different illumination modes: (1) the conventional white light mode, (2) the autofluorescence mode and (3) the ALA-induced fluorescence mode which is described elsewhere [20, 41]. The

system is based on a 300-watt Xenon lamp with special condensor optics to couple high intensities of light into a liquid light guide, which is optimized for blue light transmission. The modes can easily be switched by a pedal during bronchoscopy. In the autofluorescence mode, the wavelengths from 380 to 460 nm are used for excitation. The blue light output power at the distal end of a bronchofiberscope is typically 80 mW. For detection, most of the excitation light is blocked by a long pass filter integrated in the eyepiece of the bronchoscope. Endoscopy can be performed with flexible as well as with rigid bronchoscopy [18].

Light intensity and quality of the image of the system are excellent and allow an endoscopic orientation and investigation under direct autofluorescence guidance. The findings can be documented with a highly sensitive integrating camera which is connected directly to the ocular of the bronchoscope. Optionally and experimentally, a spectral detection of the specific autofluorescence by a beam splitter can be added [42]. An experimental online image analysis system first described by Profio et al. [43], calculates the color ratio red + blue versus green for each pixel of the image and produces a false color image. Figure 3 shows the complete system D-Light/AF with bronchoscope and camera as well as the optional spectrometer.

Finally, the system has an option for drug-induced fluorescence too: the integration of a second filter with the emission characteristic of 390–440 nm allows the detection of ALA-induced fluorescence which may be used in addition to white light and autofluorescence mode in the future [18, 20, 44].

In summary, the main advantages of the new system are: (1) the high intensity of autofluorescence light allows direct and brilliant imaging; (2) the white light and autofluorescence mode can be changed easily during bronchoscopy; (3) the costs are low, and (4) investigation of ALA-induced fluorescence is possible additionally.

Clinical Study

The system D-Light/AF was tested in a pilot study including 60 patients (44 males, 16 females) with increased risk for developing bronchial carcinoma [19]. Overall, 264 biopsies were taken. According to the criteria of the International Association of Study of Lung Cancer (IASLC) [45], patients were included as shown in table 1. Bronchoscopy was performed under local anesthesia with flexible instruments or under general anesthesia with rigid tubes in combination with flexible bronchoscopes. In some individual cases, autofluorescence detection in the trachea and the main stem bronchi was performed by rigid optical devices to obtain a better documentation. The investigation first started with white light mode switching over to blue light mode for the detection of the specific autofluorescence. Biopsies were taken from all suspicious areas detected either by white light and/or autofluorescence bronchoscopy (AFB). Additionally, in every patient, two random biopsies were taken from normal bronchial tissue. The biopsies were described in white light bronchoscopy (WLB) as well as in AFB by the following classification: (1) normal appearance, not suspicious; (2) nonspecific changes: (a) e.g. scars, granulomas, swelling, anatomical abnormalities; (b) inflammation (acute, chronic bronchitis), (c) confirmed location of preceding biopsies; (3) suspicion of malignant change, and (4) visible tumor (e.g. exophyt).

Table 1. Definition of risk patients according to IASLC

Radiological or clinical suspicion of carcinoma
Postoperative care (resected bronchial carcinoma)
Positive cytological findings
Previous positive findings of dysplasia/CIS
Known bronchial carcinoma (e.g. staging)
Smoker older than 40 years and evidence of COPD and/or occupational exposure

COPD = Chronic obstructive pulmonary disease.

The mean age of the patients investigated was 62.2 years (37–80 years). Forty-nine patients underwent bronchoscopy because of radiological or clinical suspicion on bronchial carcinoma, 4 patients had positive findings in cytology, 11 patients had undergone surgical treatment because of bronchial carcinoma.

Mean time for overall bronchoscopy was 25 min, additional autofluorescence bronchoscopy lasted 7 min on average. We found 5 cases of mild dysplasia, 6 cases of moderate to severe dysplasia, 1 case of CIS and 36 tumors. For the detection rate of dysplasia and CIS, we found a clear increase in sensitivity and for normal tissue a slight decrease in specificity. The prevalence of moderate dysplasia, severe dysplasia and CIS was 7% for WLB alone and 12% for WLB + AFB. The number of false-positive findings of 216 biopsies taken from normal tissue was small (table 2).

The positive predictive value indicates that most of the biopsies taken from suspicious areas were confirmed histologically, i.e. autofluorescence investigation caused an

Table 2. Pilot study with 60 patients and 264 biopsies

	Sensitivity		PPV dysplasia CIS/tumors	NPV dysplasia CIS/tumors	Specificity
	dysplasia/ CIS	tumors			
White light, %	33	81	72	93	94
White light + autofluorescence, %	83	83	63	96	89
Relative factor	2.80	1.03			

additional expense which was adequate to the final positive results. The high negative predictive value shows that only a few biopsies which had been judged to be nonspecific were false-negative.

The specificity was very high even if autofluorescence and white light endoscopy were combined. In autofluorescence mode, we found the same amount of false-positive biopsies characterizing inflammations or metaplasias, scars or necrotic tissue as in white light mode. In the combination WLB + AFB, the amount of false-positive results increased only slightly.

Figure 4 shows the right B2/3 carina of a heavy smoker with more than 40 pack-years. Under WLB, there are no suspicious areas while the fluorescence image shows a delimited reddish area, breaking the normal green structures. Histologically, the finding was classified as moderate dysplasia.

Figure 5 shows the middle lobe carina of a heavy smoker, which is largely inconspicuous under WLB, while the fluorescence image shows a delimited reddish-bluish area, corresponding histologically to a CIS.

Online image analysis calculates the relation between green fluorescence and red + blue reference for each pixel to quantify autofluorescence by false colors and to classify the findings [46].

Figure 6 shows an example of an autofluorescence spectrum taken from an area of severe dysplasia at the upper lobe carina and from normal tissue after excitation with blue light (380–460 nm). Both spectrums are corrected to eliminate distance dependency [47] and to quantify the autofluorescence. Excitation of tumor tissue results in a strong reduced intensity of the spectrum in the range between 500 and 600 nm. There is no difference between tumor and normal tissue for wavelengths upon 650 nm [48].

Summary of the Present Clinical and Technical Status – Future Aspects

The Drug-Induced Fluorescence Bronchoscopy

Drug-induced fluorescence is the historically older method and was developed experimentally [23]. It has, however, not been used in a considerable clinical extent up to now. The main disadvantage for the systemic application of most of the photosensitizers is a long persistent photo-sensibilization of the skin [24], especially in the case of the application of porphyrin derivatives. Pharmacological research therefore focuses on the development of new substances with higher tumor selectivity and minor retention in the skin. Very promising substances are tetra(*m*-hydroxyphenyl)chlorin [49], meso-tetra(4-carboxyphenyl)porphine [50], δ-ALA [51] and aminolevulinic esters [52]. Even in therapeutic doses, these substances are burdened with a photo-sensibilization of 2–4 days only.

δ-ALA was applied topically in a clinical pilot study [53]. First results indicate a high sensitivity for detection of dysplasia and CIS. However, a low specificity is a main disadvantage in clinical use. Low specificity is caused by an interindividually highly variable deposition and different nonspecific uptake of δ-ALA in normal and especially inflammated mucosa [41]. Trials to achieve a reproducible and homogeneous deposition in the central airways by specially developed inhalers could not solve the problem of low specificity sufficiently [53]. Although the employment of diagnostic photosensitizers is established clinically in urology [44] and neurology [54], these methods therefore cannot be transferred into clinical use in pneumology without further investigation. Finally, a main disadvantage for the drug-induced fluorescence diagnosis will remain that bronchoscopy cannot be performed spontaneously.

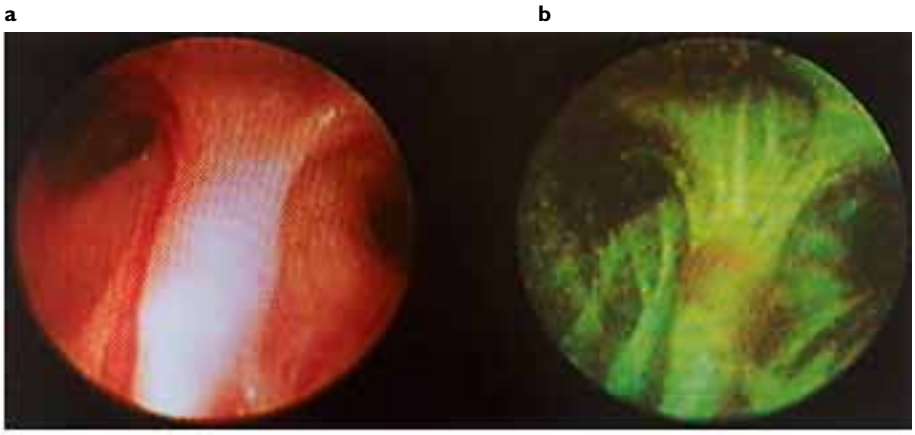

Fig. 4. Severe dyplasia. **a** White light mode. **b** Autofluorescence mode.

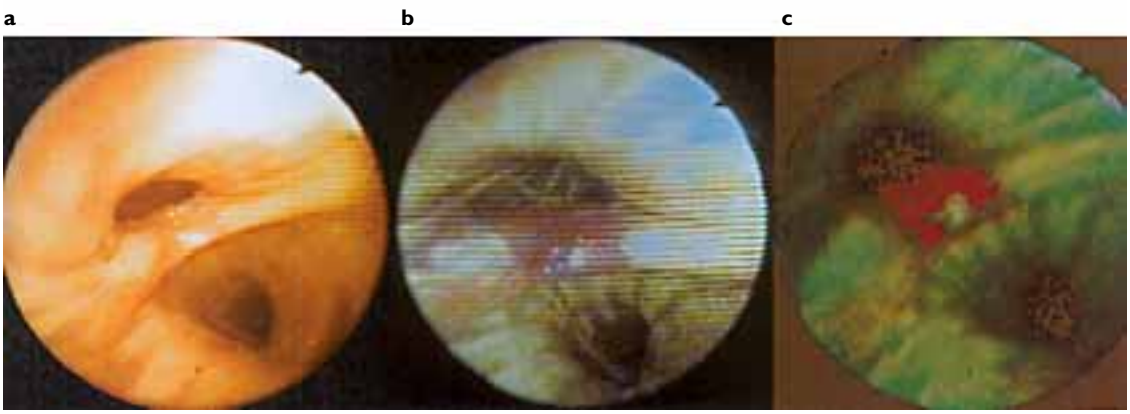

Fig. 5. Carcinoma in situ. **a** White light mode. **b** Autofluorescence mode. **c** Autofluorescence image analysis: blue color indicates low, red color indicates high reduction of autofluorescence.

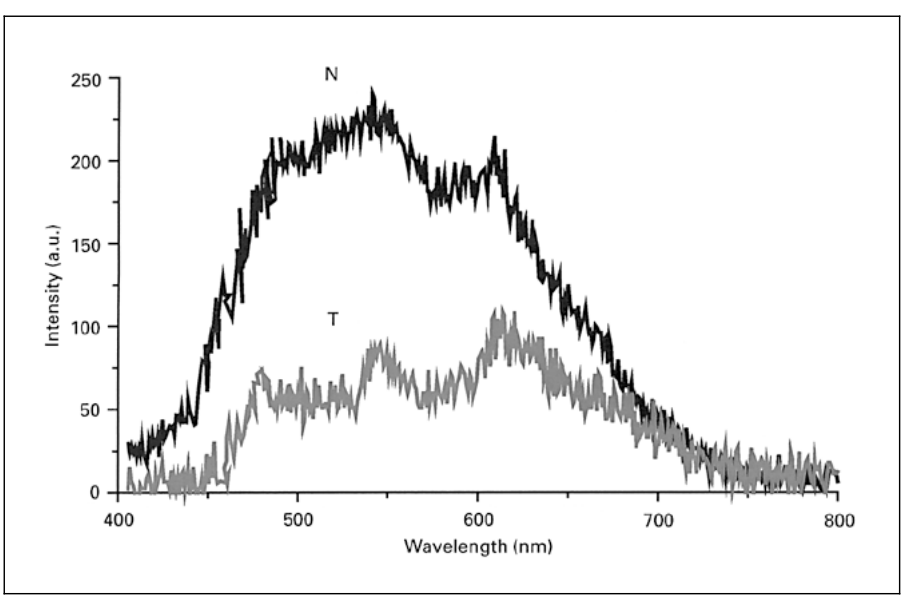

Fig. 6. Spectrum of normal (N) and neoplastic (T) epithelium.

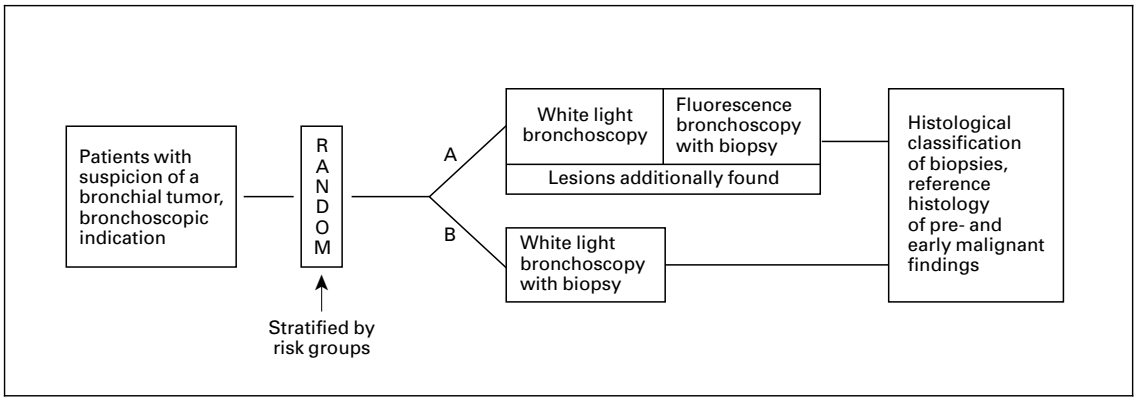

Fig. 7. Concept for a two-arm multicenter study to evaluate the diagnostic effort of the additional fluorescence detection in contrast to a normal WLB.

Autofluorescence Bronchoscopy

AFB is based on a reduction of fluorescence light within (pre-)malignant areas. This method has been introduced for clinical use by the so-called LIFE System (Xillix Corporation, Canada) [16, 28]. Disadvantages of this system are high costs, an inconvenient and weighty image intensifier camera and imaging being based only on a pseudo color on the video monitor.

At present, some developments are going on concerning technical improvements and clinical evaluation of a newly developed system. The components of this system are more convenient and are based on a modified xenon light source, on a filter on the ocular of the bronchoscope and an optional integrating camera which can be attached easily. The system allows a direct investigation by the naked eye and a quick and simple change between white light and autofluorescence mode by foot switch. Light intensity and quality of the image of this system are excellent and allow an exclusive bronchoscopical orientation and investigation under direct autofluorescence illumination.

A pilot study performed up to now yielded a similar finding rate as published in the Canadian study due to sensitivity and a slightly improved specificity. To evaluate this system, a two-armed randomized European multicenter study has been designed (fig. 7). In one arm (B), patients are investigated exclusively by white light, in the second arm WLB and AFB are combined (A). This design will help to avoid a mutual influence of the results of the specific investigation modes and to receive a realistic evaluation of the newly developed fluorescence devices for clinical use in early cancer detection.

All fluorescence bronchoscopy systems are based on individual experiences of the investigators concerning the assessment of the findings, therefore the outcome finally depends on specific and subjective clinical criteria. To eliminate this disadvantage, some technical improvements for obtaining more objective results are underway.

One possibility to obtain this target is the registration of spectra above normal, and suspicious areas to quantify their differences of light intensity objectively. A second approach is to objectify the endoscopic findings by means of electronic image analysis [55].

The most outstanding improvement of all newly developed systems, however, is most likely the dispensability of lasers and their replacement with conventional light sources. The use of filters provides an easy way of emitting the specific wavelengths, necessary to stimulate exogenous sensitizers or endogenous chromophores. Future research will increasingly focus on the use of fluorescence phenomena on a cellular level and will try to improve cytological screenings by automated sputum cytometry or by fluorescence-based methods [56]. Clinical progress and the 'vision for the period beyond the year 2000' give rise to hope that fluorescence bronchoscopy will be used as the primary method in future routine bronchoscopy.

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Interventional Bronchoscopy beyond the Year 2000

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Virtual Bronchoscopy

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Summary

Virtual bronchoscopy is still in its infancy, having been initially described in 1993. The technical aspects of data acquisition are still being refined and will continue to develop with advances in computer and scanner technology. Common current scanning protocols include spiral scanning with 3-mm collimation and a pitch of 1, with the scan volume starting at the top of the aortic arch and extending inferiorly for a single breath hold. Images are typically displayed on an independent workstation using custom or commercial software. Both surface and volume rendering are being utilized to produce virtual bronchoscopy. Virtual endoscopy in general is finding applications in screening and surgical planning. The clearest potential applications of virtual bronchoscopy are in fiberoptic bronchoscopy planning and guidance, and these are likely to drive its development. The three-dimensional images provided may allow better communication of the extent and distribution of mediastinal disease. The utility of virtual bronchoscopy as a diagnostic tool is less certain. Any advantages over axial CT must be proven and may relate to specific clinical circumstances. Teaching and training applications will continue to develop and must be tested. Limitations of virtual bronchoscopy are being identified and potential solutions developed. Particularly, the process must become more automated and accurate and less time consuming. As hardware ability to provide data overwhelms human ability to thoroughly evaluate it, virtual bronchoscopy and other computer assistance techniques may become more important. It certainly does not represent a replacement for fiberoptic bronchoscopy, but rather an adjunct. Though many limitations remain, virtual bronchoscopy is likely to prove a valuable tool in directing and improving patient care.

Virtual bronchoscopy is a rapidly developing form of virtual reality imaging, which promises to improve planning and offer guidance for interventional bronchoscopy and other diagnostic and therapeutic procedures. Based on actual patient data, usually obtained at computed tomography (CT) of the chest, virtual bronchoscopy allows the user to manipulate a computer model of a patient's airway, remarkably simulating the perspective achieved during real endoscopic procedures. This novel approach can provide information on the position of endobronchial lesions, length of stenoses, and site for transbronchial needle aspiration (TBNA) biopsy [1, 2]. It is anticipated that this information may contribute to shortened procedure times, improved biopsy yields, and better patient selection, but the ideal applications of this technologic advance have yet to be defined. Familiarity with aspects of virtual bronchoscopy technique and its early applications is important for chest clinicians as they appraise this new modality.

Technical Issues: Generating Virtual Bronchoscopy

Virtual bronchoscopy has developed as a convergence of advancing CT and computer graphics technologies. Generating accurate clinically useful airway simulations in a timely manner requires meticulous attention to aspects of data acquisition and image display.

Data Acquisition

Improvements in CT were required to generate a volume of data, rather than independent slices. Although this was possible with older scanners in stable portions of the body such as the head and extremities, motion artifacts prevented slice-to-slice registration of data for the chest and abdomen. The sources of these artifacts include breathing, swallowing, and large-scale patient motion during the relatively long (e.g. 3–5 min) scanning time required. In addition, long scan times make thinner slices less desirable. Thinner slices, created by collimating or narrowing the X-ray beam, require a larger total number of slices for complete coverage. The resulting increase in scan duration contributes to patient discomfort and reduces patient throughput. The recent development of slip-ring technology, culminating in helical ('spiral') CT scanners, allows continuous acquisition of data while the patient is moved through the scanner. A large portion of the patient can be scanned during a single breath hold, yielding a volume of data without confounding motion artifacts [3–6].

The length of scan volume is affected by several factors. These include table speed, slice collimation, X-ray tube heat capacity, and duration of breath holding. These factors also influence the quality of the data acquired. Inadequate breath holding reintroduces respiratory motion artifacts. Increased table speed or wider collimation increases the scanned volume, but also increases partial volume averaging effects. Partial volume averaging results from increasing the volume of tissue contributing to each image element and can blur edges and obscure small structures. Tube heat capacity can limit scan volume, but is usually less important than breath hold duration for chest CT. A recent development is that of multidetector spiral scanners, which promises to double to quadruple volume length without affecting other parameters.

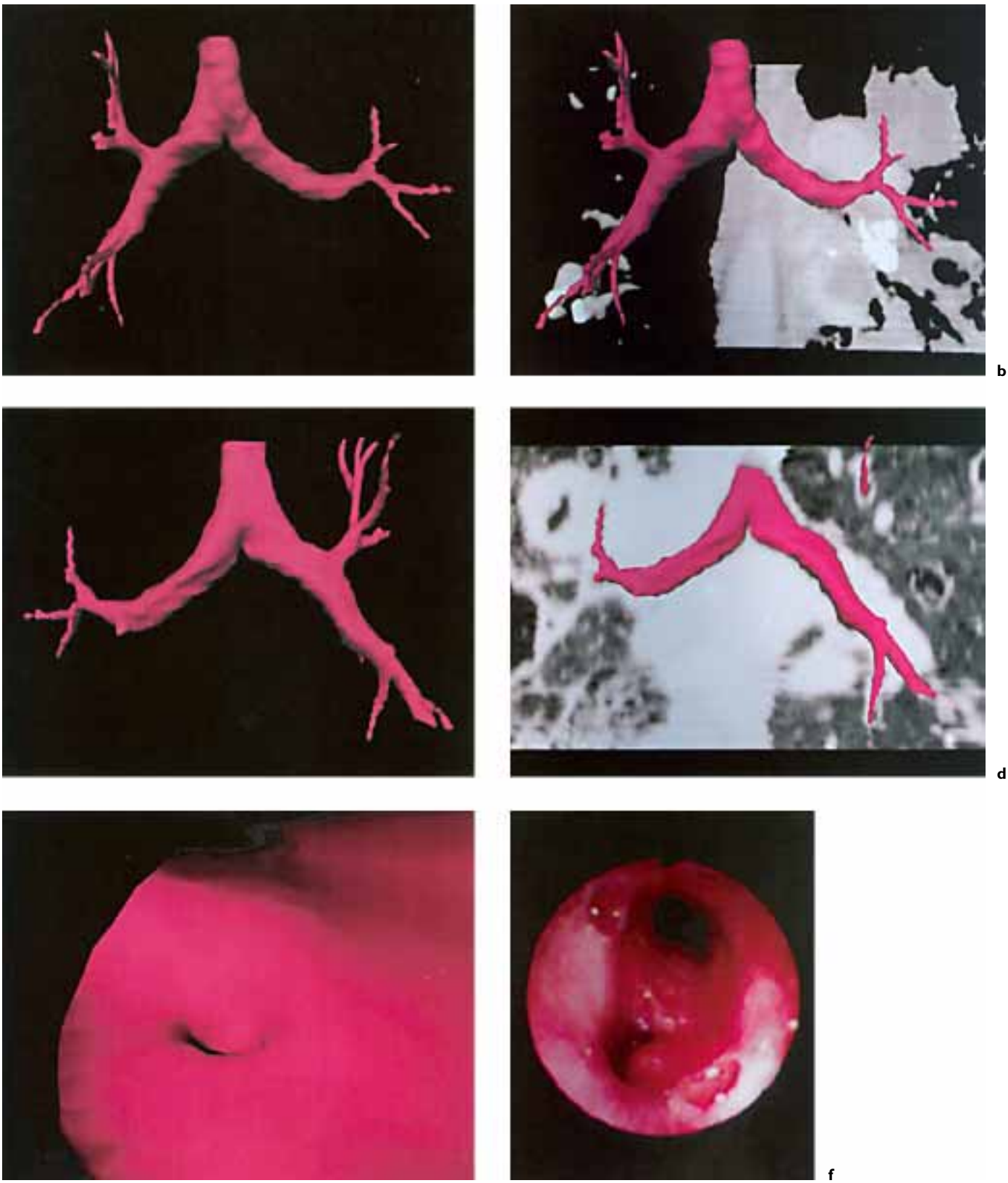
Table speed is frequently expressed as pitch, the ratio of distance of table movement per scan revolution to collimation width [3, 4]. For example, a table speed of 6 mm per scan revolution with a slice collimation of 3 mm gives a pitch of 6/3 or 2. There has been considerable investigation of the selection of appropriate combinations of pitch and collimation for generating virtual bronchoscopy images. Exact recommendations have varied with institutional preferences, but 3-mm collimation and a pitch of 1 or 1.5 are most frequently cited. Upper limits of less than 5-mm collimation and pitch of 2 or less have been suggested [7–11]. A further step to improve craniocaudal resolution is the reconstruction of overlapping images at 1- to 5-mm intervals from the raw spiral data [11, 12]. Ordinarily, image reconstruction is performed at the scanner after the patient is off the table, but it can affect patient throughput somewhat. This effect is likely to be minor compared to normal patient logistics.

Image Display

CT scan data presentation has developed with impetus from the field of computer graphics. Initially, scans were presented in the same axial format as the acquisition. Coronal, sagittal and oblique planar reformatting of the image data allowed additional views with only mild computational expense [13, 14]. The development of three-dimensional display was initially used in complex bony structures, such as the skull, hip and ankle [15–20]. Processing of CT data was performed at the scanning console and required considerable time and effort by the technologist, as well as more complex scanner software.

Much of the computing task has now been transferred to independent workstations [21]. Initially, the communication between scanner and workstation was accomplished through proprietary communication schemes, possibly including magnetic tape or other media. The recent development of the Digital Imaging and Communication in Medicine (DICOM) format and use of Internet connections allow rapid transfer of data between scanners and workstations of different manufacturers. Progress in computer manufacturing has allowed workstation prices to decrease, while computer memory and disk storage have increased. These developments have allowed the wider access and faster processing necessary to make virtual bronchoscopy practical. Workstations currently in use for virtual bronchoscopy range from small, single processor units with 64 megabytes of memory in clinical practice to multi-processor machines with one or more gigabytes of memory in research settings.

Fig. 1. Virtual bronchoscopy airway simulation. Anteroposterior (**a**, **b**) and posteroanterior (**c**, **d**) views of an airway model. Superimposed multiplanar reformatted images with soft tissue (**b**) and lung (**d**) windows show relationships to adjacent mediastinal and pulmonary structures. Endoluminal view (**e**) and fiberoptic bronchoscopy view (**f**) demonstrate correlation between these modalities.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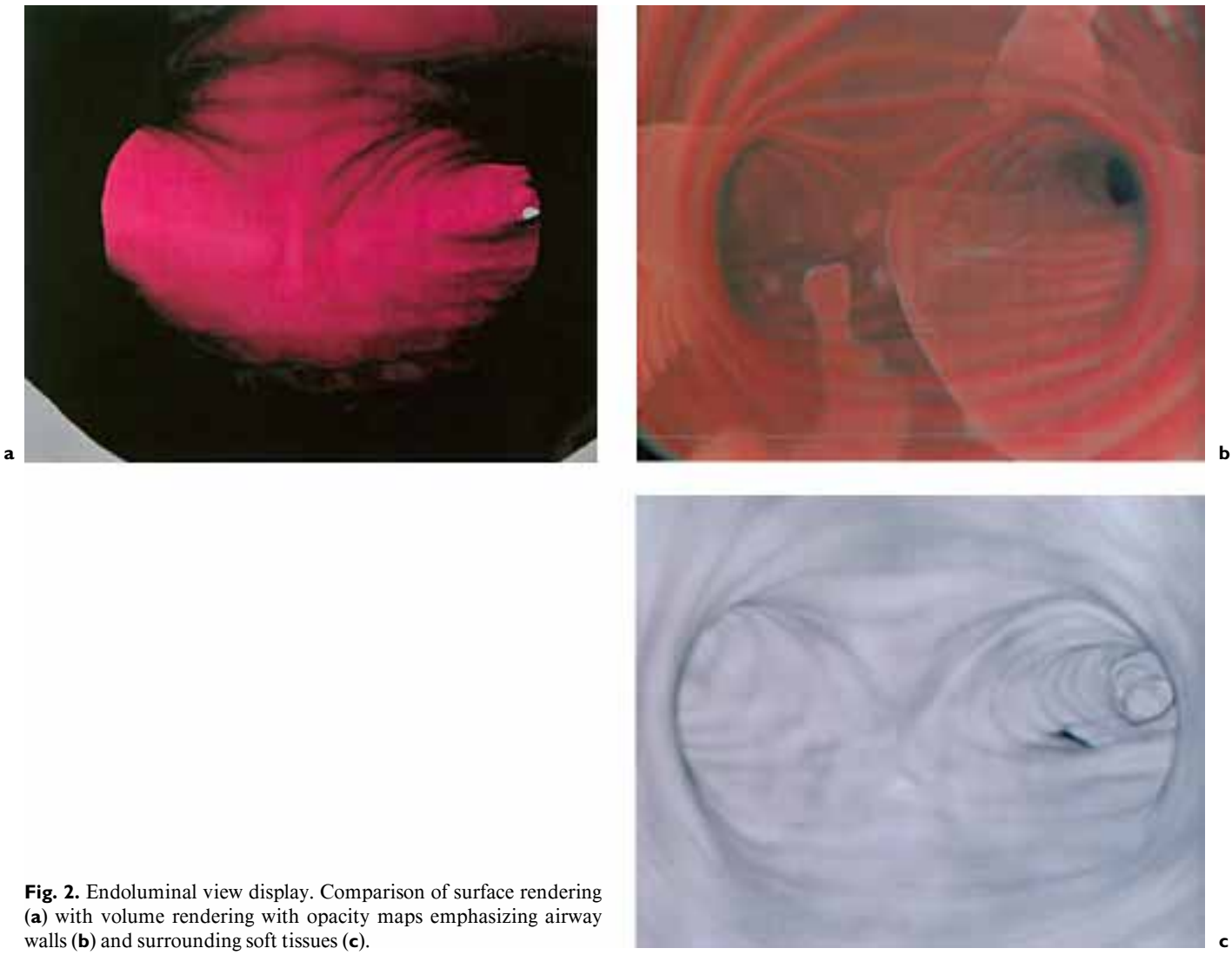


Fig. 2. Endoluminal view display. Comparison of surface rendering (**a**) with volume rendering with opacity maps emphasizing airway walls (**b**) and surrounding soft tissues (**c**).

Software progress has been essential to the development of virtual bronchoscopy. The earliest attempts at the application of three-dimensional imaging in the chest used simple thresholding to produce an external view of the lungs and tracheobronchial tree [7, 22–26]. In thresholding, volume elements (voxels) are included if the attenuation value is below a selected Hounsfield level and excluded if above this level. More advanced image editing software allowed the removal of lung structures for an unobstructed view of the airway [27]. Currently, the commonest method of identifying, or segmenting, the airway consists of selecting volume elements below a threshold which are connected to a user-selected point within the airway [28–30]. More sophisticated segmentation methods are being developed which use advanced image processing techniques [31] or incorporate some form of artificial intelligence [32, 33].

Virtual bronchoscopy allows the user to move within the airway model created from this segmentation. Images rendered from each position simulate the view through a camera at that position [30, 34, 35] (fig. 1). Other structures can also be modeled, and the airway model made partially transparent in order to demonstrate relationships to extrabronchial anatomy. Though the majority of currently available virtual bronchoscopy systems use this form of imaging, called surface rendering, yet more advanced hardware and software can produce images by volume rendering [36–38] (fig. 2). With volume render-

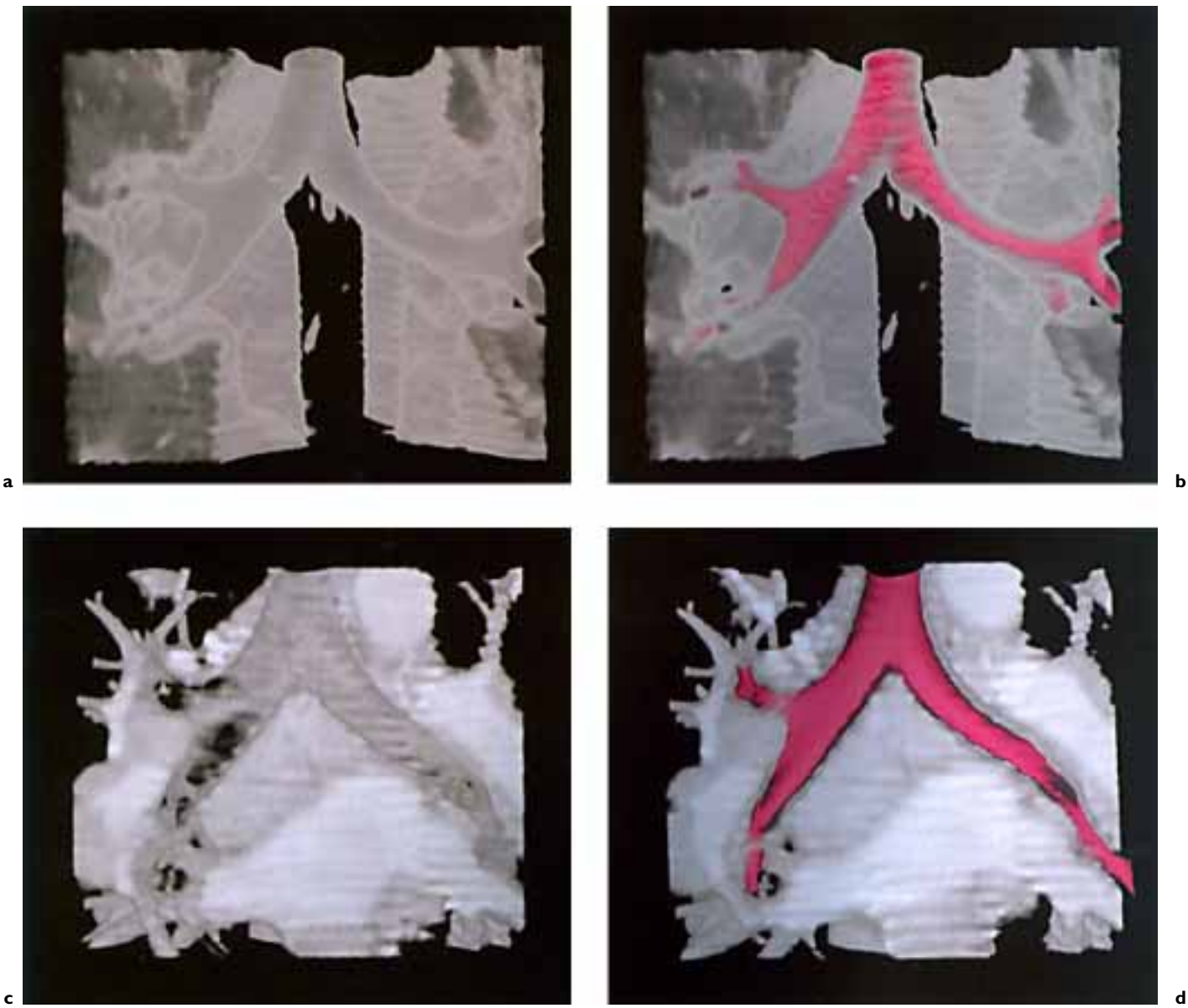


Fig. 3. Volume rendering and hybrid rendering. Volume rendering with opacity maps emphasizing airway walls (**a**, **b**) and surrounding soft tissues (**c**, **d**). Soft tissue map requires cut planes to eliminate obscuring portions of the volume. Hybrid rendering (**b**, **d**) superimposes surface rendering on volume rendering, better visualizing distal airways.

ing, opacity is calculated from CT Hounsfield units at each voxel. Airway structures are rendered as lucent while soft tissues are more opaque, allowing the elimination of the segmentation step [37]. Because volume rendering requires considerably greater computer memory and processing power to perform acceptably, this method has been used predominately in the research setting, although its use is becoming more widespread. Hybrid rendering techniques combining these approaches have also been used [29] (fig. 3).

Virtual bronchoscopy remains a labor-intensive process. Although the data transfer and rendering process may take only a few minutes, completely evaluating the airway can take much longer. In addition, without the physical cues obtained from holding the bronchoscope, the user may easily become disoriented during the view-

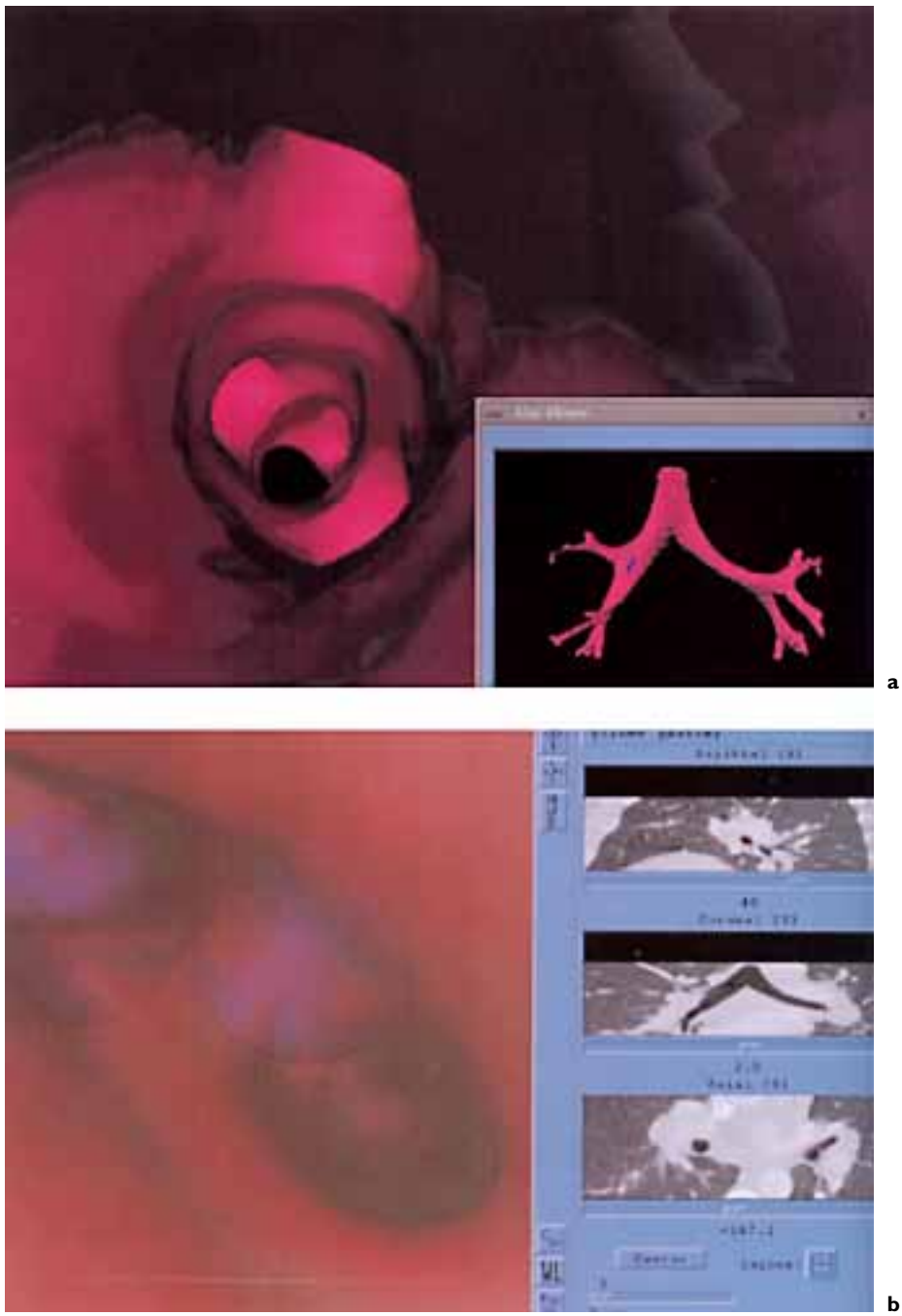


Fig. 4. Navigation aids. The map viewer, shown with surface rendering (**a**), and multiplanar reformatted images, shown with volume rendering (**b**), are used to aid orientation during bronchoscopy simulation.

ing. Tools available in different software packages include reverse views, coordinate axis display, and position and path display on separate three-dimensional images or on multiplanar reformatted images [39] (fig. 4). Virtual reality software is available from several manufacturers including CT scanner manufacturers and independent sources. Some of the commoner products and manufacturers are listed in table 1. Whether particular options assure a better overall impact upon patient care has not been established. It is likely that the approaches to virtual bronchoscopy will vary considerably with personal preferences.

Table 1. Common virtual bronchoscopy packages

Product name	Manufacturer	Platform
Navigator	General Electric Medical Systems (Milwaukee, Wisc., USA)	Advantage Workstation (Sun UltraSPARC 170E)
Voyager	Picker International (Cleveland, Ohio, USA)	Voxel Q Workstation (Sun SPARC based)
Vitrea	Vital Images (Minneapolis, Minn., USA)	Vitrea Workstation (Silicon Graphics O2)
Free flight	Wake Forest University Baptist Medical Center (Winston-Salem, N.C., USA)	Silicon Graphics Maximum Impact, Octane, or Onyx
Analyze	CNSoftware (Rochester, Minn., USA)	Various UNIX Operating-System-based Workstations

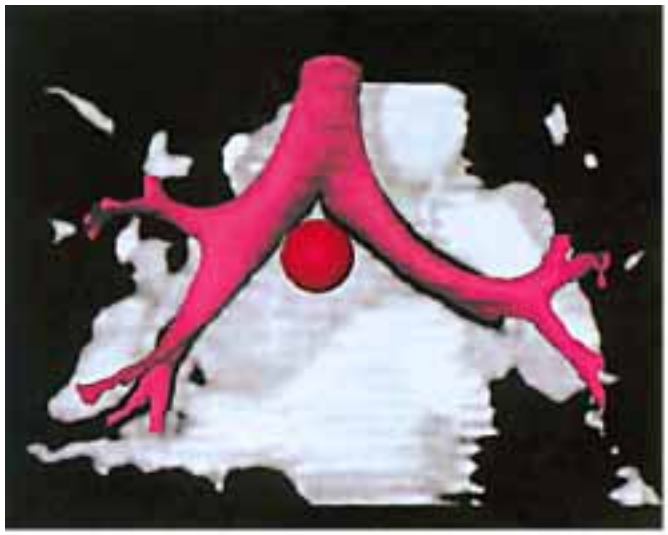
Applications of Virtual Bronchoscopy

This virtual reality process has been applied to appraising several organ systems [35, 40, 41]. The most attention has been to its use in evaluating the colon and the upper airway. Virtual colonoscopy is developing as a screening modality, potentially replacing barium enema or colonoscopy for surveillance [42–45]. To this end, more automatic methods of viewing the anatomy are being developed, as well as computer-aided lesion detection. Both of these features should be readily applicable to the airway. Virtual endoscopy in the nose and sinuses is being used for planning of functional endoscopic sinus surgery [46]. Virtual laryngoscopy has been used to evaluate for subglottic tumor extent, potentially guiding selection of patients for hemilaryngectomy rather than total laryngectomy [47, 48]. Other virtual reality endeavors, such as cystoscopy, angioscopy and spinoscopy are helping demonstrate the potential of this technology for preprocedure planning [49–52].

Procedure Planning

Procedure planning for fiberoptic bronchoscopy has been provided by several imaging modalities. Chest radiographs are usually the initial method for visualizing intrathoracic structures. Unfortunately, only limited information is available from the radiograph to assist in bronchoscopy planning. Laterality, lobe, and segmental distribution can be obtained in some cases, usually those with fairly significant disease. Radiographs are also poor at detecting endobronchial disease, and at defining the extent and location of adenopathy. Standard CT provides much more information. Subtle parenchymal disease can be easily detected. Bronchial abnormalities, such as endobronchial lesions and bronchiectasis, can also be evaluated. The size and distribution of mediastinal and hilar adenopathy can be quantified. Suspicious areas can often be localized to the segmental level and beyond, and sites for TBNA biopsy selected with some accuracy [1, 2]. However, limitations to the utility of CT in guiding bronchoscopy remain. Oblique structures are more difficult to adequately assess, especially if measurements in an oblique plane are needed. Thinner sections or reconstructions may be of some help, but this approach can lead to an overwhelming number of images. In addition, it can sometimes be difficult to appreciate three-dimensional relationships from axial images.

The development of three-dimensional rendering techniques, including virtual bronchoscopy, offers a method for overcoming some of these difficulties [12]. External surface rendering of the airway has shown improvement in detecting airway stenosis compared to axial CT in some cases [27]. Virtual bronchoscopy has similarly been shown to be effective in demonstrating airway pathology [13, 53–55], with a high concordance between major endobronchial disease demonstrated at airway simulations with findings visualized at fiberoptic bronchoscopy [56]. Large-scale trials have yet to be performed to quantify the accuracy of virtual bronchoscopy and its relative contribution compared to CT. Part of the reason for this is that the technology, both for scanning and display, continue to advance, and consensus regarding the optimum procedure has not yet been reached.



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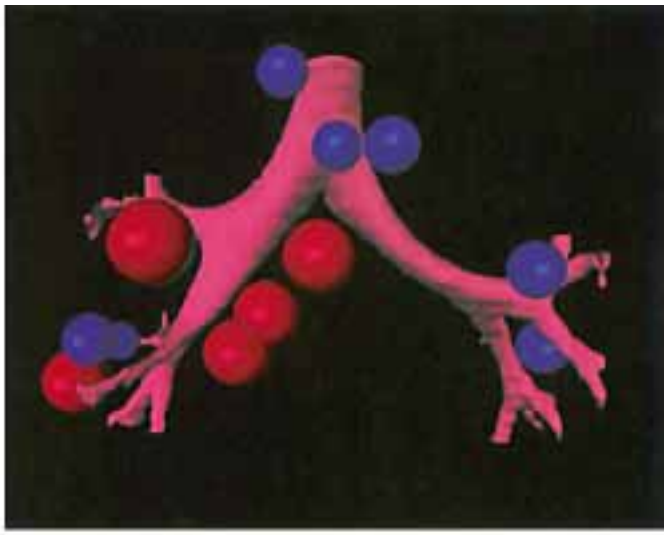

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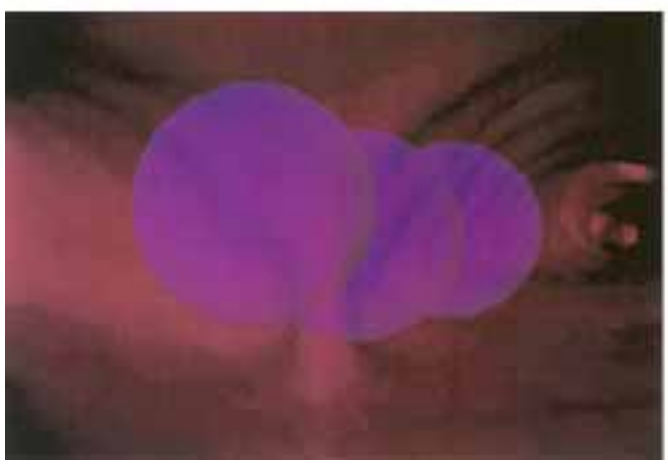

6a

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Fig. 5. Lymph node modeling. Spherical targets used to model lymph nodes are placed and sized with the aid of multiplanar reformatted image (**a**). Target colors (**b**) are used to indicated lymph nodes smaller (blue) and larger (red) than 1.5 cm.

Fig. 6. Bronchoscopy simulation with lymph node models. Surface rendering with transparency (**a**) or volume rendering (**b**) can be used to show an endoluminal perspective for transbronchial needle biopsy planning.

Procedure planning uses for virtual bronchoscopy include evaluating endobronchial lesions and selecting sites for airway sampling [2]. Endobronchial lesions can be difficult to fully assess on axial images. Virtual bronchoscopy can add measurement of cross-sectional area and length of stenosis that cannot be calculated directly in the axial plane and may be difficult to estimate during bronchoscopy [1]. This quantitative information can be especially worthwhile in planning endobronchial stent placement, laser photocoagulation, cryotherapy and brachytherapy procedures [57]. Secondary areas of airway obstruction distal to the primary lesion can be seen at virtual bronchoscopy even if the more proximal lesion cannot be crossed endoscopically [58]. This information may affect therapy selections by altering the expected benefit of an endobronchial intervention. Planning of endobronchial sampling methods, such as brushing, washings or forceps biopsy might also be improved, particularly as the rendering of more distal bronchi is improved. Selection of the site of highest likelihood of positive yield could shorten procedure times, potentially reducing complications. Follow-up after endobronchial intervention may be another

role for virtual bronchoscopy. The assessment of response or recurrence of major abnormalities after therapy may be adequate with virtual imaging along, with fiberoptic bronchoscopy reserved for repeat interventions as needed [59].

An additional application of virtual bronchoscopy is in lung cancer staging [60]. Adenopathy may be segmented or modeled to demonstrate its distribution in the hila and mediastinum (fig. 5). This information could influence the selection among percutaneous, mediastinoscopic or bronchoscopic approaches, as well as aiding in planning these procedures. The improved perspective concordance afforded by virtual bronchoscopy can particularly aid in the selection of TBNA biopsy sites [2]. Accurate measurements from anatomic landmarks such as the carina or lobar bronchi origins can be combined with directional indication given as clock positions [1]. Axial images are simply unable to provide this type of information and are limited to anatomic directions (anterior, posterior, inferior, etc.) which may be difficult to apply from an endobronchial perspective. Rendering extrabronchial structures through translucent airway walls can provide a reference image of the proposed biopsy site [1, 56] (fig. 6). This type of information might be most helpful at institutions where TBNA yield is low, but might also provide some benefit at other centers. Smaller and more difficult targets might be sampled with this form of procedure planning.

Procedure Guidance

Real-time procedure guidance of TBNA biopsy by virtual bronchoscopy is an application only beginning to be explored. Currently, the majority of image guidance of bronchoscopy is achieved with fluoroscopy. Fluoroscopic guidance is most helpful in the distal airways, especially for brushings or forceps biopsies performed beyond the limits of direct fiberoptic visualization. Under fluoroscopy, accurate selection of bronchial paths to peripheral pulmonary nodules can be difficult due to the overlapping of structures. CT guidance of bronchoscopy has been described, enhancing the ability to direct forceps or brushes to far distal lesions [61] or confirming the needle position at TBNA [62, 63]. In this case, bronchoscopy is performed in the CT scanner. While this approach still has the limitations of axial images, for very small peripheral lesions it may improve biopsy success. The visual confirmation of contact between the biopsy instrument and the lesion may be most helpful in nonmalignant lesions by increasing confidence in the sampling process [63].

One proposed solution to biopsy guidance is through the use of previously acquired virtual bronchoscopy data registered to the patient during fiberoptic bronchoscopy. The position of the fiberoptic instrument is then superimposed on the virtual bronchoscopy data. When the endoscope tip is positioned correctly with respect to the extrabronchial lesion, biopsy is performed. Hardware and software solutions to this registration problem are under development. The former involves a positioning sensor (e.g. Biosense, Cordis Webster Inc., Baldwin Park, Calif., USA) placed at the tip of the endoscope [64]. The position, angle and rotation of the sensor can be determined and this information used to update the virtual bronchoscope position. The software approach involves an image-matching process that determines the fiberoptic endoscope position from its video output [65].

Once the fiberoptic endoscope position is obtained, the virtual bronchoscopy view from that point is calculated. These images could be displayed in the bronchoscopy suite alongside the endoscopic image, complimenting the widespread use of television monitors displaying images acquired with video computer chip bronchoscopes. By rendering the simulated airway walls translucent, the bronchoscopist could see when the target mass or lymph node was directly ahead and proceed with the biopsy. An alternative is to have audible feedback in the form of an alarm, which would increase in pitch or volume as the lesion was approached. A distinct shift in the alarm pitch or volume when the projected needle path enters the target lesion would be the signal for sampling. An advantage of this method is that the bronchoscopist would not have to shift attention between two monitors [66].

Real-time CT scanning, also known as fluoro-CT, involves subsequent acquisition and reconstruction of CT images. This technique allows real-time imaging at up to 8 frames per second during the procedure, for improved guidance [62]. Multidetector scanners promise to deliver real-time volumetric acquisition and allow virtual bronchoscopy data to be updated during the procedure, obviating the need for a registration step. This capability would represent the highest level of accuracy in imaging guidance.

Applications to Education and Training

In addition to its direct roles in patient care, virtual bronchoscopy has great potential in education, endoscopy training and procedure rehearsal [67]. In anatomy teaching, virtual bronchoscopy and three-dimensional rendering can present a more understandable and interactive method for presenting anatomic relationships. This approach is being realized (e.g. The Dissectable Human; Engineering Animations Inc., Ames, Iowa, USA) using

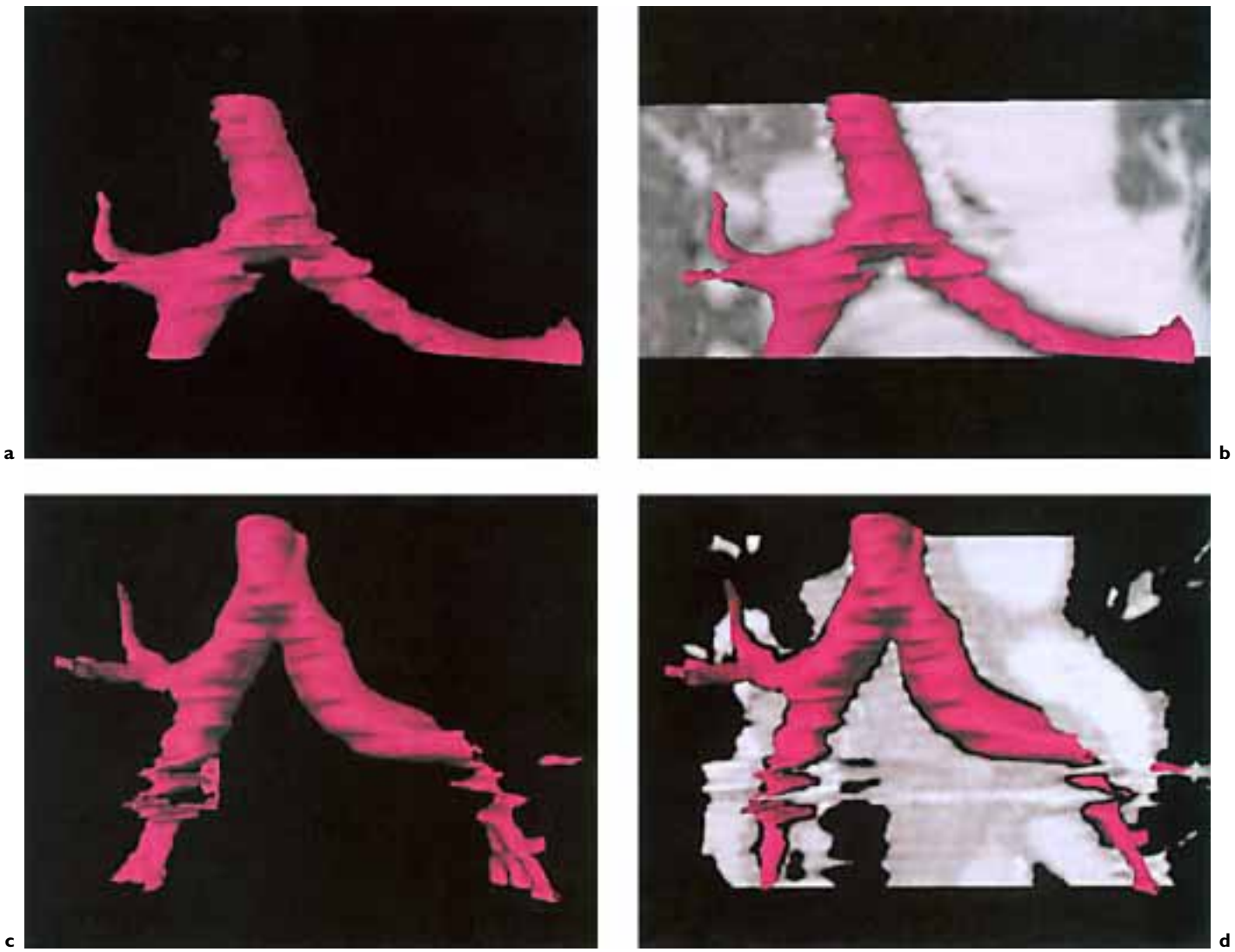
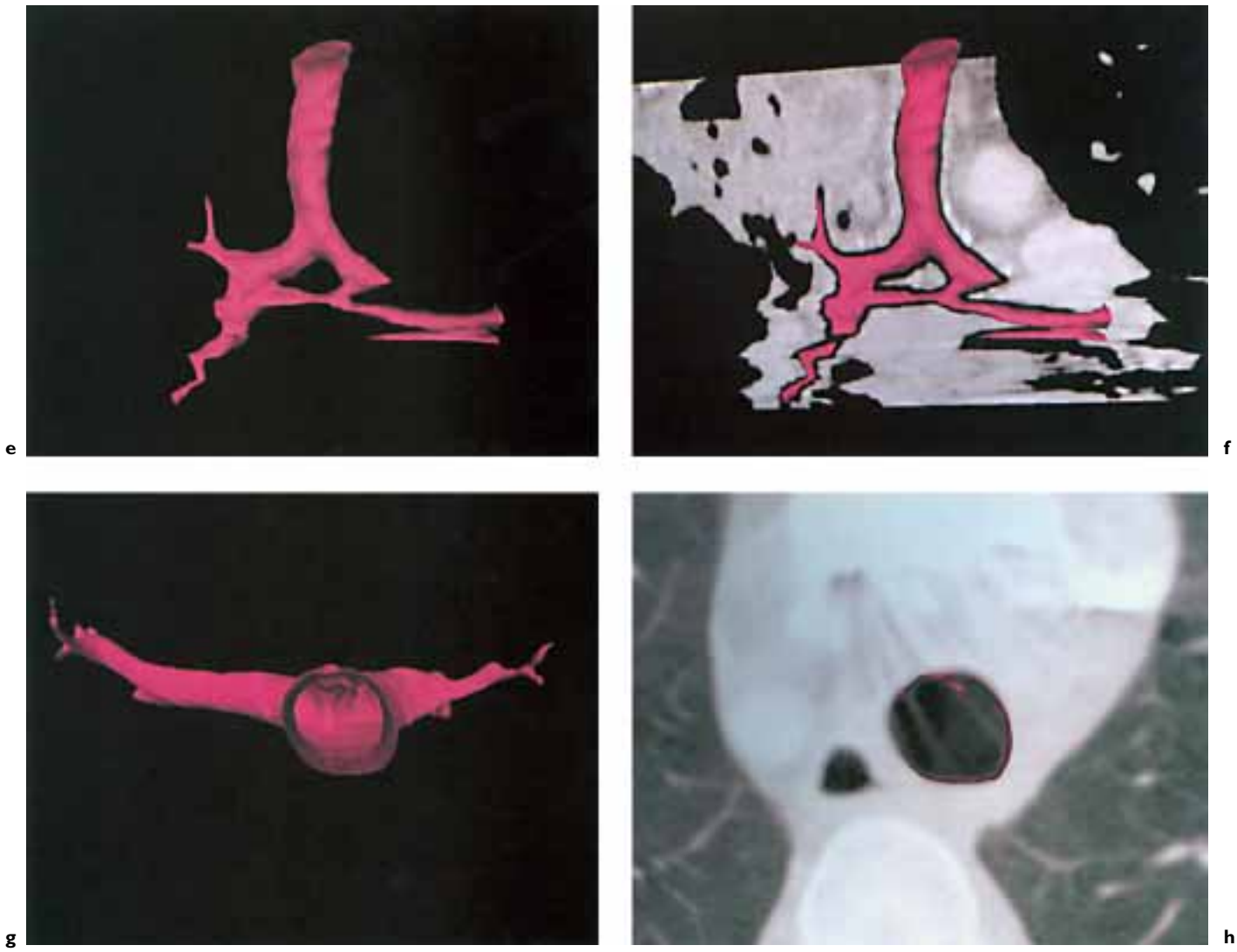


Fig. 7. Artifacts. Airway models (**a**, **c**, **e**, **g**) and superimposed multiplanar reformatted images (**b**, **d**, **f**, **h**) demonstrate causes of artifacts. Respiratory motion (**a**, **b**) causes moderate distortion of the airway model. Cardiac pulsation (**c**, **d**) disrupts the airway model at the level of the left atrium. Large-scale motion due to coughing (**e**, **f**) causes severe distortion of the airway model. Streak artifact due to contrast bolus (**g**, **h**) primarily affects low segmentation thresholds.

data from the Visible Human project (United States National Library of Medicine, Bethesda, Md., USA). Features include structure labels and the ability to make various structures visible as needed. A bronchoscopy training device (PreOp Endoscopy Simulator; HT Medical, Rockville, Md., USA) has been developed, again based on the Visible Human dataset, and includes a realistic bronchoscope and simulated patient. As the bronchoscope is passed into the patient, the endoscopic view is rendered. This complex simulator includes respiratory and cardiac motion, coughing, secretions, hemorrhage and a variety of airway lesions. Both diagnostic and interventional procedures can be simulated.

Several methods of training, combined with experience, have been shown to improve TBNA yields [68, 69]. The fluency in use of a simulator has been shown to discriminate experience levels among users [70], and suggests that practice with such a simulator may be an effective training method. Because some research suggests that the majority of endoscopic complications occur early in an operator's experience [71], virtual bronchoscopy training may offer a reduction in overall complications. With



the ability to import real patient data into a simulator, patient-specific procedure rehearsal could be performed. Though the benefit of this strategy remains to be defined, it may affect both procedure time and patient selection.

Limitations and Future Development

Much work remains to be done in the field of virtual bronchoscopy and virtual endoscopy in general. Study is required to establish the sensitivity and specificity for the procedure in its diagnostic applications [13, 53–56] and is likely to be an ongoing process as further refinements are developed. The benefit of virtual bronchoscopy compared to standard helical CT must be evaluated critically in various clinical situations [14], and the optimal techniques must be determined and updated as technology advances. Several artifacts must be addressed and minimized [11, 12, 58]. The most important of these is patient motion, especially respiratory and cardiac. The contrast bolus can cause streak artifact, and its appropriate timing must be defined (fig. 7).

Another important limitation of virtual bronchoscopy is its inability to provide mucosal detail [72]. At this point, there is no foreseeable method to address this. The clinical implications of this lack of mucosal information must be considered as the applications of virtual bronchoscopy are evaluated further.

Time and equipment requirements have a large impact on the utility and availability of virtual bronchoscopy. Equipment costs have fallen, but are still not inconsequential. This problem should continue to improve as prices fall. Independent consoles are becoming more commoner for monitoring and rapid review of examinations. Many of these are capable of rendering virtual bronchoscopy, though often with relatively long processing times. The segmentation step frequently requires some human interaction, which also increases time requirements. Furthermore, the viewing process is time consuming for the physician, and whether this commitment is justified by clear-cut benefits for the patient requires evaluation. Finally, it is difficult to insure that all of the anatomy is actually seen during the viewing session.

Many of these limitations are being addressed. Automatic segmentation methods, which accurately identify more distal airways, are being developed. Viewing path algorithms can be used to produce a movie that visualizes all mucosal surfaces. The movie is created offline, reducing required viewing time while assuring completeness. Computer-assisted lesion detection, successfully applied in virtual colonoscopy [73, 74], promises to improve the reliability of virtual bronchoscopy findings. Analyses of wall thickness and surface curvature have been proposed as methods of identifying tracheobronchial abnormalities [75]. Motion compensation and cardiac gating of CT data may reduce artifacts. Registration of serial examinations could be used to identify subtle interval change. Significant hurdles remain in each of these developing areas.

Hardware improvements will also aid in the accuracy and utility of virtual bronchoscopy. Multidetector scanners will reduce examination times to levels tolerable by all but the most dyspneic patients. Falling computer costs, accompanied by increasing processing power, can make virtual bronchoscopy more widely available. Development of simulators that accept patient data may make virtual bronchoscopy review quicker and more meaningful to bronchoscopists. Availability of fluoro-CT and real-time virtual rendering could make imaging guidance of procedures more accurate and useful.

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Optical Diagnostic and Therapeutic Technologies in Pulmonary Medicine

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Summary

This chapter describes optical diagnostic and therapeutic technologies. Some are currently available, while others are still in the research and development phase. Diagnostic technologies involve spectroscopic techniques such as fluorescence, elastic scattering, Raman and infrared spectroscopies. Fluorescence spectroscopy includes methods of detecting endogeneous fluorophores in tissue (autofluorescence) as well as exogenous fluorophores. Currently available systems using laser-induced fluorescence have been clinically used. Other technologies are currently being investigated: elastic scattering technique and Raman and infrared spectroscopic techniques. These technologies are complementary to autofluorescence and can be used for diagnosing dysplasia and early lung cancer. Optical imaging and tomography include optical endoscopic imaging and optical coherence tomography as well as confocal and multiphoton microscopy. Optical therapeutic technologies include interstitial laser thermotherapy as well as photodynamic therapy. Most of these technologies are currently investigated in laboratory settings and may be clinically used in the near future.

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Background

Lung cancer, which accounts for 25% of all cancer deaths, is currently the most common cause of cancer death among men and women in the US. It is projected that by 2004, there will be twice as many women who will die of lung cancer than of breast cancer. Long-term survival for patients with lung cancer has not changed significantly in the last 20 years. The majority of patients are diagnosed at an advanced stage, and most of the research has been aiming at treating the advanced disease. However, treatments at this advanced stage have not been shown to make a significant difference in improving survival over the last two decades.

Current efforts aimed at preventing or stopping smoking activities in teenagers and young adults are a high priority and have been receiving increasing interest. However, a different strategy based on early diagnostics should

be applied to the older age groups in order to achieve a significant reduction in lung cancer mortality. One reason for this latter strategy is based on the fact that long-term heavy smokers carry a substantial lung cancer risk even years after smoking cessation [1, 2]. Nowadays, over 50% of patients with lung cancer are former smokers, many of whom had stopped smoking for 5 years or more [1, 2]. The success of cervical cytology and screening mammography programs in reducing the mortality associated with cervical and breast cancers promises some hope that a similar strategy of early detection and intervention will also bring about a significant reduction in lung cancer mortality [3].

Currently, there is no rapid, practical and effective screening test available for lung cancer. Advances in computer-assisted image analysis and optical imaging technologies make it possible to reexamine the issue of early diagnosis and treatment in order to improve the outcome of patients with lung cancer. The stage of premalignant epithelium places the patient at risk for carcinoma, usually by the development of dysplasia, starting from low-grade to high-grade dysplasia [4, 5]. This stepwise progression has provided the basis to survey premalignant epithelium by random biopsies, which are then submitted to histological interpretation by a pathologist [6]. Unfortunately, panels of experts have poor agreement on the interpretation of such biopsies, particularly for the severest and highest risk samples such as high-grade dysphasia or carcinoma in situ (CIS) [7, 8]. In addition, biopsies carry some inherent risk since they are invasive. In an effort to measure the premalignant progression from normal epithelium to high-grade dysphasia in an objective manner, epithelial biopsies have been analyzed using flow cytometry and assayed for biomarkers of such pre-malignant changes, including measuring for the *p53* mutant protein [9]. Recent development of DNA biochip technologies could provide the much-needed tools that can be used in the physician's office to detect genetic markers such as the *p53* gene mutation [10, 11].

Patients at high risk for lung cancer are generally surveyed with multiple random biopsies at specified intervals and with more intensive sampling of any suspicious areas that are visually evident. A major drawback of this approach is the known difficulty in recognizing objective visual clues that unambiguously indicate the presence of a significant histologic abnormality. If the epithelium at risk is rigorously excised via physical biopsy, the histologic and molecular biologic properties can be mapped out. However, dysplastic and cancerous changes are potentially present at many hidden locations in the epithelium at risk such that there is often no visual indication available to the endoscopist. It is often difficult to detect and localize early cancers, e.g. CIS and pre-neoplastic lesions using white light broncoscopy. In a previous study, it was reported that the site of CIS lesions could be localized only in approximately 40% of the cases investigated [12]. There is an urgent need for an objective and accurate method capable of detecting these hidden abnormalities reliably so that precancer and cancer occurrence can be directly treated at the earliest, and presumably, most curable stage. The non-invasive or minimally invasive nature of optical technologies makes them most attractive for both early diagnostic and therapeutic applications.

Optical Diagnostic Technologies

Optical technologies can provide a powerful means for detecting early neoplastic changes. The detection of early neoplastic changes is important from an outcome viewpoint, since once invasive carcinoma and metastases have occurred, treatment is difficult. At present, excisional biopsy followed by histology is considered to be the 'gold standard' for the diagnosis of early neoplastic changes and carcinoma. In some cases, cytology rather than excisional biopsy is performed. These techniques are powerful diagnostic tools because they provide high-resolution spatial and morphological information of the cellular and subcellular structures of tissues. The use of staining and processing can enhance contrast and specificity of histopathology. However, both of these diagnostic procedures require physical removal of specimens followed by tissue processing in the laboratory. As such, these procedures incur a relatively high cost because specimen handling is required and, more importantly, diagnostic information is not available in real time. Moreover, in the context of detecting early neoplastic changes, both excisional biopsy and cytology can have unacceptable false-negative rates often arising from sampling errors.

Optical technologies have the potential capability of performing in situ diagnosis on tissue without the need for sample excision and processing. This diagnostic information can be available in real time. In addition, since removal of tissue is not required for optical diagnostics, a more complete examination of the organ of interest can be achieved than with excisional biopsy or cytology. Currently, one of the major challenges in the development of optical technologies in neoplastic diagnosis is to develop protocols and algorithms which permit raw data produced with an optical diagnostic tool to identify dysplasia and neoplasia.

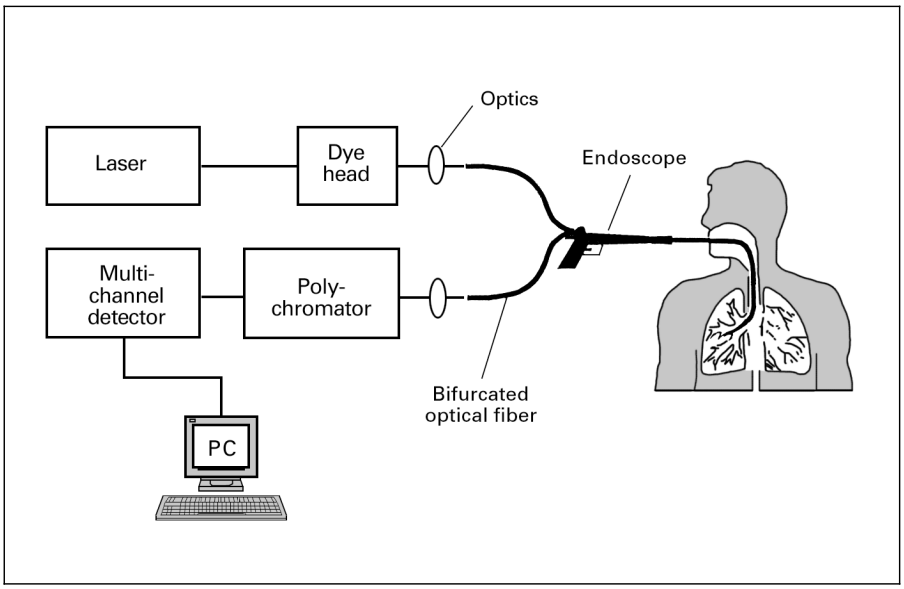

Fig. 1. Schematic diagram of a LIF system for use in lung cancer diagnostics.

Another important application for optical diagnostic technologies is the possible use of these techniques for guidance of surgical intervention and treatment. In such assistance applications, the ability of optical diagnostic technologies to provide real-time information is critically useful. The optical diagnostic approaches may either be an imaging modality or a spectroscopic modality. In either case, but especially with the imaging modality, one can provide more precise guidance of surgical intervention. The spectroscopic diagnostics may also be used to provide real-time assessment of tissue response to therapy. An example would be the assessment of tissue viability and necrosis in thermal, laser interstitial therapy or photodynamic therapy (PDT).

Currently used optical diagnostic technologies can be broadly classified into two categories: (1) spectroscopic diagnostics and (2) optical imaging, often referred to as optical tomography. These two categories will be discussed later. Spectroscopic diagnostic techniques are generally used to obtain an entire spectrum of a single tissue site within a wavelength region of interest. These techniques are often referred to as point-measurement methods. On the other hand, optical imaging methods are aimed at recording a two-dimensional image of an area of the sample of interest at one specific wavelength. A third category, which combines the two modalities, is currently in an early development phase. This category, often referred to as multi-spectral imaging or hyperspectral imaging, will also be discussed.

Spectroscopic Diagnostic Technologies

Spectroscopic diagnostics all share the common feature that they measure some spectroscopic properties that are related to the molecular composition and structure of biochemical species in the tissue of interest. There are several spectrocopic methods that are used for optical diagnostics: fluorescence, elastic scattering, Raman (inelastic scattering) and infrared absorption.

Fluorescence Spectroscopy. Fluorescence methods can be grouped into two main categories: (1) methods that detect endogenous fluorophores of tissues, often referred to as autofluorescence; and (2) methods that detect or use exogenous fluorophores or fluorophore precursors (such as 5-aminolevulinic acid, ALA). In other words, the fluorescence may originate from native fluorescent chromophores already present in the tissue or from an administered exogenous chromophore that has been specifically synthesized so that it targets specific tissue (e.g. dysplasia versus normal) or is activated by functional changes in the tissue. The approach using exogenous chromophores can be applied not only to fluorescence but also to other spectroscopic techniques and will be discussed later. This section mainly discusses the autofluorescence method that involves detection of the fluorescence emission signal from the tissue itself, reflecting variations in the biochemistry of the tissue, as reflected in changes in fluorescent chromophores. The tissue is exposed to excitation light at some specific wavelength (typically near ultraviolet or visible), which excites tis-

sue molecules and induces fluorescence emission from these molecules; the emission spectrum (emission intensity versus wavelength) is then measured by varying the emission wavelength.

A number of investigators have investigated laser-induced fluorescence (LIF) as a method to discriminate tumors from normal tissues, and diagnostic methods for the lung can benefit from the extensive research conducted for detecting cancer in other organs. LIF spectroscopy is a powerful technique that can potentially be used to noninvasively examine tissue fluorescence spectral signatures. Figure 1 shows a schematic diagram of an LIF system for lung diagnostics. The LIF technique has been used to characterize pre-malignant colorectal lesions and to distinguish adenomatous polyps from normal colon tissue and hyperplastic polyps [13]. LIF was also used to distinguish adenomatous tissue from normal colon tissue in vivo [14] and to investigate the origin of the spectral differences between normal and cancerous lung and breast tissues [15]. A method using excitation-emission matrices has been investigated to find the optimum excitation wavelength for fluorescence diagnosis of colon dysplasia [16]. An analysis method using fluorescence data was used to distinguish neoplastic tissue from nonneoplastic tissue [17]. Clinical studies using LIF have shown high accuracy in differentiating normal and malignant esophageal tissues using 410-nm excitation [18–21]. Various aspects of LIF techniques in imaging and point measurement systems for cancer diagnosis have been described recently [22–30].

Elastic Scattering Technique. The elastic scattering (ES) technique involves detection of the backscattering of a broad-band light source irradiating the tissue. A spectrometer records the back-scattered light at various wavelengths and produces a spectrum that is dependent on tissue structure as well as chromophore constituents. Tissue structure is the parameter a pathologist assesses in performing diagnosis using histological examination. In general, the tissue is illuminated with the excitation light launched into a specific point location via an optical fiber and the scattered light is measured from a nearby location. Since light is strongly scattered in tissue, which is a highly diffusing medium, the mean free path for anisotropic scattering is in the order of several microns. Therefore, the scattering path of photons is generally described by a stochastic process of many random steps. Calculations based on Monte Carlo methods have been used to investigate the photon scattering process. In some variations of this type of methodology, the optical transport properties of the tissue can be measured directly. The physical quantities that are measured in this diagnostic technique are the absorption and scattering properties of the tissue and/or the wavelength dependence of these properties. The ES technique has been developed for in vivo cancer diagnostics [31, 32].

Raman and Infrared Spectroscopic Techniques. Raman scattering (RS) and infrared (IR) absorption spectroscopies are vibrational techniques, which typically have high specificity because they provide vibrational information intimately related to molecular structures. Thus, the Raman technique can also be used for qualitative identification of organic compounds using chemical group frequencies and scatter intensities. The selection rules and relative intensities of IR and Raman peaks are not similar, so that RS and IR spectroscopies are often viewed as complementary. With IR spectroscopy, the ever-present intense absorption bands of water (present in all biological samples), which overlap with most of the other tissue component spectra, severely hamper IR spectroscopy.

In the case of Raman spectroscopy, due to the intrinsically weak Raman cross-section, the magnitude of the Raman scattering is typically small, making either high-illumination intensities or relatively long measurement times necessary [33–35]. Although Raman spectroscopy is increasingly being used for quantitative analysis, there are a number of obstacles to overcome before Raman techniques can routinely match the accuracy, precision, and ease of use of more mature analytical methods. Two important components of any reliable analytical method are reproducibility and sensitivity. Although any light source can be used, the intrinsically low intensity of Raman scattered radiation generally requires the use of laser radiation as the excitation source and, in fact, the use of Raman spectroscopy has increased significantly since the development of high-powered, continuous-wave gas ion lasers (e.g. argon and krypton ion lasers) in the late 1960s. Raman spectroscopy has been investigated for diagnostics of other organs, but this technique has not been implemented clinically in lung diagnostics.

Optical Imaging and Tomography

Optical Endoscopic Imaging. The second category of optical medical diagnostics is optical imaging and tomography. A method using ratio fluorescence imaging [22] has been developed to obtain images of tissues at different wavelengths. Fluorescence bronchoscopy is an imaging technology that can provide an improved tool to determine the location of cancer using autofluorescence [26–30]. The Light Imaging Fluorescence Endoscopic device

(LIFE-Lung) is the first optical imaging endoscopic device since the development of white-light reflectance bronchoscopy that has been approved by the Food and Drugs Administration in the US and elsewhere (Canada, Europe and Japan) to enhance the detection and localization of preinvasive lung cancer [30]. Clinical trials worldwide in over 1,000 patients showed that fluorescence bronchoscopy can improve the detection rate of preinvasive lung lesions by several times compared with conventional white light examination. Lesions as small as 1–2 mm can be detected by this method. Potential application of this technology in other sites such as the esophagus, colon, urinary bladder, cervix and oral cavity requires further research and development.

Confocal and Multiphoton Confocal Microscopy. Confocal and multiphoton confocal microscopy use the spatial focusing properties of light in order to obtain depth information or to enhance imaging in optically scattering tissues. These imaging technologies produce very high resolution images. Recent advances in multiphoton confocal microscopy use short-pulse illumination and multiphoton excitation of chromophores [36]. These multiphoton techniques yield enhanced imaging depth and enable imaging of living cells with reduced photobleaching effects. These technologies represent one of the major recent advances in optical microscopy and have been used extensively in research. Clinical application requires further development of endoscopic light delivery and collection systems.

Optical Coherence Tomography. Optical coherence tomography (OCT) is a technique, which provides cross-sectional images of tissue in situ. OCT is analogous to ultrasound B mode imaging that allows high-resolution cross-section imaging of the tissue microstructure. Instead of acoustic waves, OCT uses light and performs imaging by measuring the backscattered intensity of light from structures in tissues. In contrast to ultrasound, because the velocity of light is extremely high, the echo time delay of reflected light cannot be measured directly. Interferometric detection techniques must therefore be used [37]. An optical beam is focused into the tissue; the echo time delay of light reflected from the microstructure at different depths is measured by interferometry. Image information is obtained by performing repeated axial measurements at different transverse positions as the optical beam is scanned across the tissue. The resulting data yield a two-dimensional map of backscattering or reflectance from internal architectural morphology and cellular structure in the tissue. The axial resolution is 10 μm, i.e. up to ten times higher than any clinically available diagnostic modality. A device could be constructed with a fiberoptic probe, which can be incorporated into catheter-based or endoscopic systems.

The 'histology-like' images are obtained in real time with no need for excision, and thus this technique has potential for diagnosis of early neoplasia and surgical guidance. It is largely still a research technique, although it has been introduced into clinical applications in ophthalmology. OCT was originally developed and applied to tomographic diagnostics in ophthalmology. OCT can provide images of the retina with resolutions of 10 μm. Imaging depth is limited by optical attenuation due to scattering and absorption. OCT has been applied in vitro to image arterial pathology where it can differentiate plaque morphology with a resolution superior to that obtained with ultrasound. OCT is a promising imaging technology because it can permit real-time and in situ visualization of tissue microstructure without the need to excisionally remove and process a specimen as in conventional biopsy and histopathology. However, the current resolution is only 2–3 mm deep, thus the bronchial thickness of 8 mm may pose a problem.

OCT can provide a diagnostic tool complementary to spectroscopic techniques and has great potential for in situ microscopic imaging of cellular attributes of malignancies and precancers, which rivals that of a histopathologist examining a tissue biopsy specimen under a microscope. While cell-staining techniques have not yet been designed to be visualized with this technique for use by the histopathologist, the orientation of the tissue within a three-dimensional matrix and the measurement of the sizes of cellular and subcellular elements in vivo can provide unique information and insights into the dysplastic and malignant processes and can be linked, just like tissue spectroscopy probes, to therapeutic procedures once a suspicious area is identified. Development is ongoing to make these probes small and flexible enough to be employed endoscopically.

Photon Migration Techniques. Photon migration techniques can be used to perform point measurements or imaging measurements in deep tissues (several centimeters) by using multiply scattered light. Great interest has been directed to time-resolved and phase-resolved in vivo spectroscopy, particularly the measurement of the probability distribution of times for photons to travel from one point on a tissue surface to another [38]. The time delay of the photons coming out from another point on the surface a few centimeters away can be measured by using picosecond laser pulses launched into the tissue via optical fibers. The transit time is the optical path length divided

by the speed of light in the tissue medium, and the attenuation of the signal intensity is due to the absorption within the tissue through which the light has migrated. The attenuation of the signal due to absorption depends on the molar extinction coefficient, the path length, and the concentration of the absorption species. Since the first two factors can be determined, these measurements might provide useful values of the concentration of the absorbing molecules. These techniques take advantage of the fact that light at near IR wavelengths is not highly absorbed by tissue and thus can penetrate several centimeters. Multiple scattering of the light degrades image information, so most of these techniques either focus on low-resolution imaging or functional assessment of tissue at low-resolution. Because tissues are very strong diffusers of light, the mean free path between anisotropic scattering is in the order of 50 μm, and the light is almost completely randomized within 1 mm. Thus, for distances between two points in tissue greater than 1 mm, the migration of photons may be adequately described by a random walk of many steps. Various methods and instrumentation based on time domain techniques [39, 40] and frequency domain techniques [41–43] have been investigated to elucidate various aspects related to photon migration in tissues.

There has recently been great interest in theoretical studies to develop mathematical methods to reconstruct the image of tissues using photon migration techniques [44]. In the frequency domain techniques, the incident light is intensity modulated, thus producing a photon number density which oscillates in space and time. The resultant photon density waves scatter from tissue inhomogeneities (e.g. tumors in a tissue volume), and these scattered waves, if properly recorded, can be used to reconstruct the unknown inhomogeneity distribution into a two-dimensional image. The intensity-modulated photon density waves obey a Helmholtz equation, and several investigators have attempted to exploit this fact to derive image reconstruction equations, using mathematical models analogous to that of ultrasonic diffraction tomography. Recent theoretical studies have been performed to derive a complete and explicit solution to this inverse problem of image reconstruction for diffraction tomography [45].

Other Techniques

Optical Diagnostics Using Exogenous Chromophores or Precursors. Although the method based on the detection of exogenous chromophores can be applied to all of the spectroscopic techniques described previously, LIF spectroscopy has been used for diagnosis of cancer in conjunction with photosensitizers such as hematoporphyrin derivatives (HPD), fluorescein and indocyanin green [46]. A spectroscope system has been developed to analyze HPD fluorescence in early stages of cancer of the lung, stomach, skin, urinary bladder and cervix in humans [47]. A krypton laser was used to excite fluorescence and an intensified optical multichannel analyzer was used for analysis of the fluorescence spectra. HPD-specific fluorescence of the cancer tissues was clearly demonstrated. An endoscopic technique was described for photographic and visual detection of the laser-induced fluorescence of photofrin™ using helium-cadmium laser excitation at 442 nm [48]. The detection system was a flexible fiber bronchoscope equipped with a camera for long exposure photography. A review of this diagnostic technique has discussed different excitation light sources, detection systems and the minimum dose of photosensitizer required to exceed background autofluorescence [49]. There is also great interest in using fluorophores synthesized in the tissue after external administration of a precursor molecule, specifically protoporphyrin IX induced by ALA [50]. The chromophores discussed previously have all been used in clinical studies of fluorescence diagnostics [51–56]. Fluorescence spectra in lung tissue resulting from photosensitizer injections have been investigated [55, 56].

It is noteworthy that, with the use of certain chromophores, a possible disadvantage of using photosensitizers for diagnosis of malignancies is skin photosensitivity for several weeks, requiring the patients to avoid sunlight. However, this problem is not relevant to lung diagnostics since the lung is not exposed to sunlight.

Synchronous Luminescence for Cancer Diagnostics. Synchronous luminescence is a unique approach that could improve the selectivity of fluorescence techniques for cancer diagnostics. As discussed previously, autofluorescence of neoplastic and normal tissues has been observed using fixed-wavelength laser excitation. However, the use of fixed-excitation might not be sufficiently selective in some diagnostic applications due to strong overlap of the emission spectra from different fluorophores. An alternative approach is the synchronous luminescence method, which involves scanning both excitation and emission wavelength simultaneously while keeping a constant wavelength interval between them [57, 58]. This method, also referred to as synchronous fluorescence (SF), has been developed for multicomponent analysis and has been used to obtain fingerprints of real-life samples and for enhancing selectivity in the assay of complex

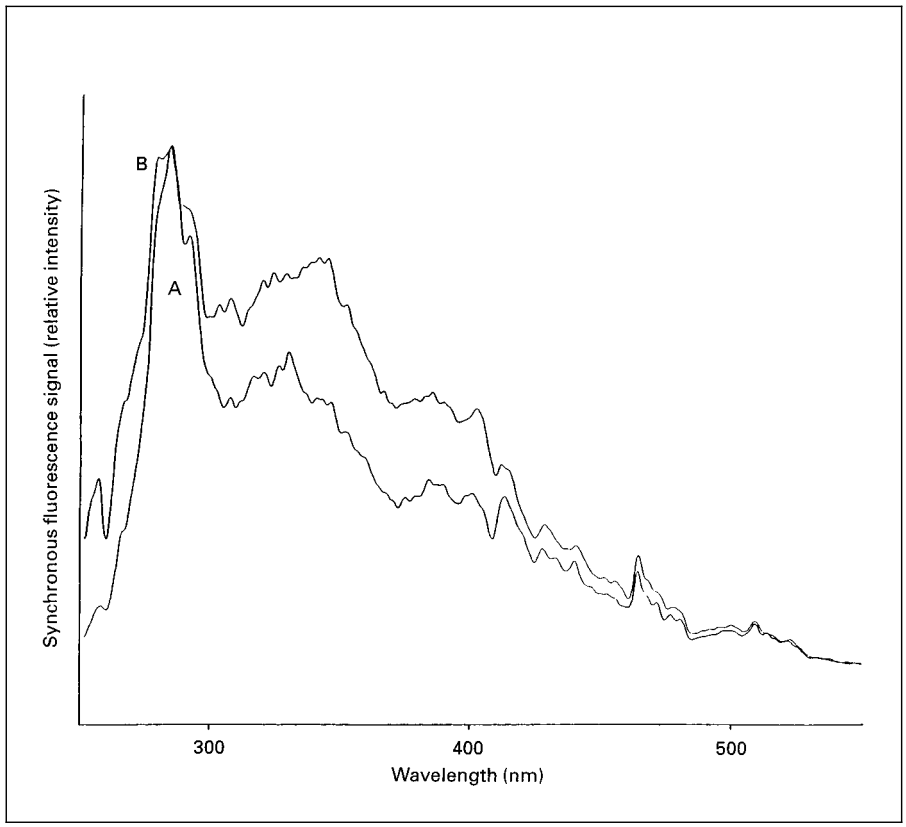

Fig. 2. Differences in spectral signatures of normal rat liver epithelial (A) and neoplastic McA cells (B) using synchronous fluorescence (wavelength difference: 20 nm).

systems. This SF procedure has been shown to simplify the emission spectrum and provides for greater selectivity when measuring the fluorescence or phosphorescence from mixtures of compounds [57]. Spectral differences in SF emission profiles are related to the specific macromolecule(s) that differed between neoplastic and normal cells. The SF method has been investigated as a rapid screening tool for monitoring DNA damage (DNA adduct metabolites) in animal studies, thus providing a technique for early cancer prescreening at the DNA level [59]. The SF technique has been shown to improve spectral selectivity in detecting normal and cancer cells for potential use in biomedical diagnostics [60]. Whereas conventional fixed-excitation fluorescence could not show any differentiation between normal and cancerous cell lines, spectral difference between the fluorescence spectra of the normal rat liver epithelial and neoplastic rat hepatoma McA cell lines was detected using SF (fig. 2) [60]. The results demonstrated the great potential of SF as an improved screening tool for cancer diagnosis in specific cases where conventional fixed-excitation methods are not sufficiently effective.

Multispectral Imaging. Spectral imaging represents a hybrid modality for optical diagnostics, which obtains spectroscopic information and renders it in image form. In principle, almost any spectroscopic method can also be combined with imaging. Some of these techniques use computer-based image processing in combination with microscopy. These techniques have had a major impact on research and are being implemented in cytological diagnostics. There is also considerable future potential for direct clinical applications. The concept of multispectral imaging (MSI) is illustrated in figure 3. With conventional imaging, the optical emission from every pixel of an image can be recorded, but only at a specific wavelength or spectral bandpass. With conventional spectroscopy, the signal at every wavelength within a spectral range can be recorded, but for only a single analyte spot. On the other hand, the MSI concept combines these two recording modalities and allows recording the entire emission for every pixel on the entire image in the field of view with the use of a rapid-scanning solid-state device, such as the acousto-optic tunable filter (AOTF). An MSI device using an AOTF has been developed [61, 62] and was used as a

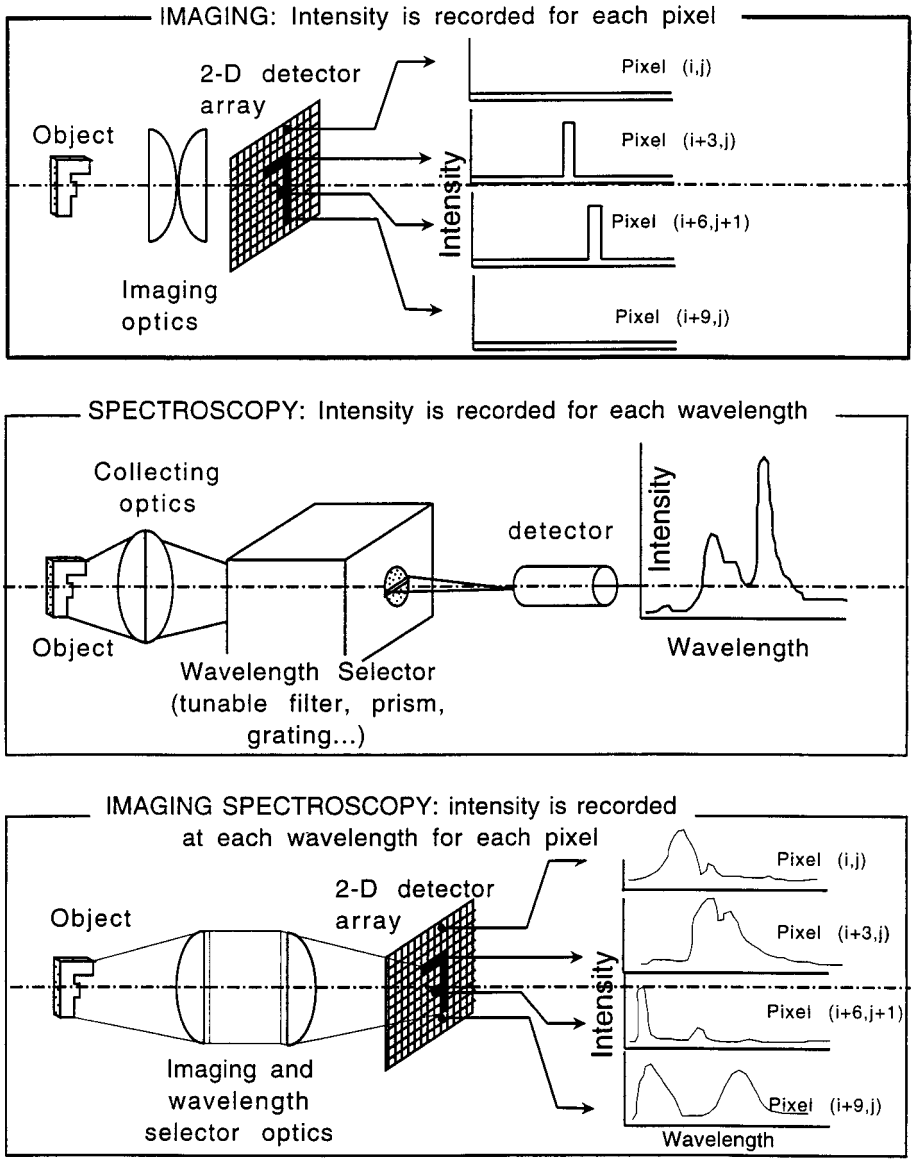

Fig. 3. Concept of multi-spectral imaging.

rapid-scanning wavelength selector. Figure 4 shows a schematic diagram of an MSI system developed to record the entire two-dimensional image of rat brain tissue [61]. A two-dimensional charge-coupled device (CCD) was used as a detector. The AOTF was used as a wavelength selector. Unlike a tunable grating or prism-based monochromator, the tunable filter has no moving parts, and it can be rapidly tuned to any wavelength in its operating range. The large aperture of the AOTF and its high spatial resolution allows the optical image from an imaging fiberoptic probe to be recorded by the CCD. These characteristics, combined with their small size, make AOTFs important new alternatives to conventional monochromators, especially for spectral imaging in biomedical applications.

Functional Assessment. Functional assessment techniques also combine spectroscopic measurements with imaging. In some cases, these techniques combine spectroscopy with photon migration in order to perform functional assessment of deep tissue structures. One example is the spectroscopic detection of oxy- and deoxy-hemoglobin for noninvasive assessment of tissue oxygenation. This application is being transferred to clinical practice.

Point Probe Systems versus Two-Dimensional Imaging Systems

Current systems having point monitor probes can provide quantitative data on certain tissue properties such as fluorescence emission, and elastic/nonelastic scattering. These point probe devices are generally less costly than imaging devices. They hold the promise to characterize and quantify important biochemical and/or structural properties of tissues for clinical diagnosis or monitoring. For rapid screening, the complex topology of the bronchial passages renders a point monitoring strategy less practical than an imaging modality that can obtain information for a larger area. However, vast areas of the lung that consist of bronchial microchannels, are not accessible to the relatively large imaging endoscope probe; therefore, the use of a point probe when passed to a distal area under image guidance could be most appropriate to provide the needed information in bronchial diagnostics. It is obvious that a device that combines an imaging probe and point probe system may be an ideal system. To confirm the diagnosis, fine-needle aspiration biopsy or transbronchoscopic biopsy may be also required. This procedure, even under CT guidance, is difficult for small lung nodules under 1 cm in size. Needle biopsy or thoracoscopic lung biopsy is uncomfortable for the patient and carries a significant risk of morbidity. A potential solution for localizing small peripheral lung nodules, is to develop smaller bronchoscopes with resolution as good as the currently available finger-size bronchoscopes. This would allow access to regions of interest. One should also develop a 'smart needle' with a point probe that can interrogate the tissue deep into bronchial passages.

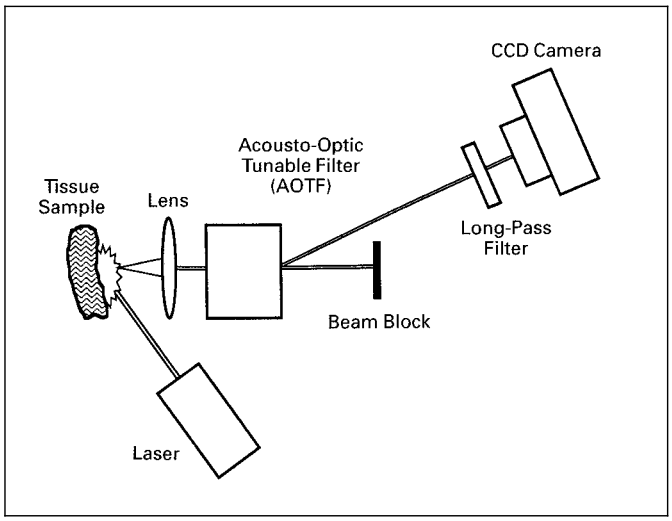

Fig. 4. Schematic diagram of a multispectral imaging system using on AOTF for medical diagnostics.

Optical Therapeutic Technologies

In addition to optical diagnostics, optical techniques are used for therapy in specific applications. The unique features, advantages and limitations of these optical diagnostic techniques are discussed in the following sections.

Reduction of Invasiveness of Surgical Procedures

By virtue of the way that they are delivered, optical therapeutic techniques can often reduce the invasiveness of conventional surgical procedures, or enable new procedures that are not possible with conventional surgical tools. For example, interstitial laser thermotherapy (ILT) has the potential to replace surgical excision in several applications. The ILT procedure typically involves a light-diffusing fiber tip to deliver laser light (typically near-infrared) to a volume of tissue in order to gently heat the tissue to the point of denaturing proteins and DNA, generally at temperatures $\sim$60–90°C. This 'gentle' heating is designed to prevent tissue carbonization and vaporization, thus permitting the body's immune system to gradually remove the dead cells over a period of time. ILT has recently been approved for treatment of benign prostatic hyperplasia, as an outpatient procedure. In general, due to the availability of fiberoptic light delivery systems, laser therapeutics have the advantage that they can be performed in conjunction with many existing surgical or diagnostic modalities and tools such as endoscopes, trocars or catheters. With laser surgery, precision of therapeutic protocols can be enhanced because control of laser exposure parameters can be used to control the therapeutic process. For surgical applications, effects ranging from thermal cautery with hemostasis to precision ablation can be achieved.

Treatment where the Locus of Treatment Requires Selectivity

The precise control of the wavelength as well as temporal and power parameters of laser therapeutic techniques can restrict the interaction to specific target areas of tissue. This important feature is beginning to be used in dermatology, where careful control of laser parameters permits selective destruction of specific loci in the skin, for example in tattoo removal, treatment of port-wine stains, and various cosmetic applications.

An important application of optical technologies for site-selective therapy is the use of PDT [46, 63]. With PDT, a photoactive compound with some degree of selective affinity for cancerous tissue is administered topically, orally or intravenously. After a period of time (typically 6–48 h), the compound has concentrated selectively in areas of malignancy. The molecule is then photoactivated with light at a specific wavelength, producing singlet oxygen preferentially in malignant tissues. Although the exact mechanism of cell death is still under investigation, it has been shown that the presence of singlet oxygen in cells has a cytotoxic effect on the target cells. PDT is being investigated for applications in several clinical areas including skin cancer, bladder cancer, carcinoma of the GI tract and lung cancer.

An essential parameter in photodynamic therapy is the preferential uptake of the photosensitizer by neoplastic tissue. Photodynamic therapy is most beneficial if the light is delivered when the concentration of photosensitizer in tumor tissue is greater than that of adjacent normal tissue. Photosensitizer concentration in tissue may be determined by chemically extracting the drug from the tissue. These techniques involve collection of a tissue sample, homogenization in an alkaline solution, and centrifugation followed by spectrofluorometric examination of the supernatant [64, 65]. The amount of tissue required for such a procedure is often prohibitive in a clinical environment, and the limited sensitivity of the assay precludes accurate analysis of biopsy-sized samples. While such techniques are currently available for photosensitizer quantitation in tissue for basic studies, they are considered invasive, time consuming and often clinically unpractical.

Development of a noninvasive technique to estimate photosensitizer concentration in tissue, preferably in real time, is desirable. While fluorescence of photosensitizers may be used to localize tumors, it does not provide a quantitative measure of drug concentration in normal and tumor tissue. It is desirable to develop a noninvasive technique to quantitate photosensitizer concentration in tissue. A prototype instrument was designed to measure in vivo photosensitizer concentration [66]. This technique is based on measuring the spectrum of diffusely reflected light from tissue surfaces and identifying the characteristic absorption spectrum of the photosensitizer. The feasibility of this technique was demonstrated in the detection of phthalocyanine in tissue. The relationship between the in vivo fluorescence signal and the concentration of phthalocyanine in rat tissue has been studied for PDT treatment [67]. This allowed an estimation of drug concentration from fluorescence intensity measurements. It should be emphasized that an estimation of drug concentration based on fluorescence intensity is under the assumption that the optical properties of each tissue type are identical among all samples. Further studies are needed to develop expressions between LIF intensity and photosensitizer concentration for each normal and malignant tissue.

Discussion

With all these spectroscopic techniques, the optical measurements are used to characterize a state of the tissue. This characterization can relate to pathology, such as the detection and grading of early neoplastic changes, or can relate to functionality, such as the determination of tissue viability and treatment margins in laser interstitial therapy. Many of these spectroscopic techniques can also be combined with imaging so that images of diseased tissue sites versus normal sites can be constructed. Thus, these diagnostic techniques inherently provide superior coverage and thus minimize sampling errors, which often occur with biopsy or cytology. Real-time diagnostic information is a significant added benefit. At this early stage of development, spectroscopic diagnostic techniques have to be verified by comparison with pathology, the current 'gold standard', which itself varies in reliability. Thus, sensitivity and specificity of spectroscopic diagnostics depends upon the reliability of pathology in each specific desired application.

Evidence is mounting that molecular events come before morphological changes. Thus a standardized classification of preclinical morphological change, while beneficial, may not actually monitor the earliest stages of carcinogenesis. If 'optical biopsy' is going to have a role in clinical diagnosis, the problem becomes what gold standard we are going to use for calibrating the optical measurements. Using pathology as the gold standard for intraepithelial neoplasia (preinvasive cancer) has its own difficulties. Substantial variation exists among pathologists in the diagnosis of preinvasive cancer. Pathologists often disagree on their interpretation of these lesions, with the level of consistency varying for different organs. Therefore, building decision-making boundaries using optical measurements that are based on conventional pathology will encounter limitations due to the variability of that gold standard. Since both under- and over-diagnosis are undesirable, it is imperative that objective and standardized pathological classification systems be established for grad-

ing preinvasive lesions for each separate organ area where these new technologies may be applied. In addition, long-term outcome studies will be valuable in assessing the predictive capability of these new technologies, which may exceed that of the current standard. It is anticipated that optical diagnostic techniques have a great potential to provide noninvasive or minimally invasive screening tools that can rapidly identify 'hot spots' that would be further analyzed for pathology.

Another potentially important opportunity for optical technologies lies in the noninvasive measurement of the concentrations of various drugs and biological species in tissues. This capability would provide a variety of benefits in medical research. A specific example of such a benefit is the case of chemotherapy drugs used for the treatment of various cancers. While the therapeutic benefit is determined by the tissue concentration of the drug in the targeted organ or site, the only minimally invasive check available to the oncologist is to track the blood serum concentration and to assume a relationship between the amount of drugs at the target organs and the tissue concentration. More generally, the ability to track compound concentrations in tissue noninvasively would be a tremendous advantage. Optical methods could bypass much of the tedious and time-consuming trials that attempt to relate dosage to metabolic rates and target organ concentrations.

In conclusion, from a clinical standpoint, optical technologies such as LIF, ES, RS and OCT have the ability to provide rapid in vivo interpretation. Sensitivity and specificity in various organ systems will be the deciding factor on which technology is best for each organ or epithelium. Combination of these technologies may be important for improving sensitivity and specificity. For instance, LIF can be used to generate a real-time pseudo image on a viewing monitor by using radio fluorescence imaging, thereby expressing malignant or dysplastic regions in a distinctly different color than normal surrounding tissue. Large areas of epithelium could be rapidly prescreened with this technique so that when an island of hot spot epithelium is identified, then the prescreening can be confirmed by spectroscopic techniques (LIF, ES, RS or OCT) using point probes that are placed in contact with the abnormal region identified in the prescreening phase. The combination of these new optical technologies will be extremely useful for elucidating the underlying processes of various diseases and for increasing the accuracy, sensitivity and specificity of diagnostic and therapeutic features. One single technique may not be able to achieve these levels of accuracy, but a combination of techniques, such as radio fluorescence imaging endoscopy to screen large areas of epithelium followed by confirmation of abnormal areas by spectroscopic probe-based techniques such as LIF, ES, RS and/or OCT could provide an effective diagnostic modality. With these combined detection modalities, new information can be gathered, thus improving our understanding of the basic pathophysiology of not only cancers, but also other nonmalignant diseases, such as benign structures and inflammatory diseases whose mechanisms are currently poorly understood. Finally, recent advances in biochip technologies, which combine biotechnology concepts and silicon fabrication technology, could lead to the development of inexpensive, portable or hand-held devices that can be used in the physician's office for rapid cancer screening by detecting genetic markers. Figure 5 shows such an integrated circuit sensing system of a DNA biochip for detecting a variety of pathogens and diseases [10, 11]. The cost saving with improved quality healthcare could be achieved even if only one promise of optical diagnostic technologies is realized, that of reducing the number of required (often random, costly and unnecessary) surgical biopsies.

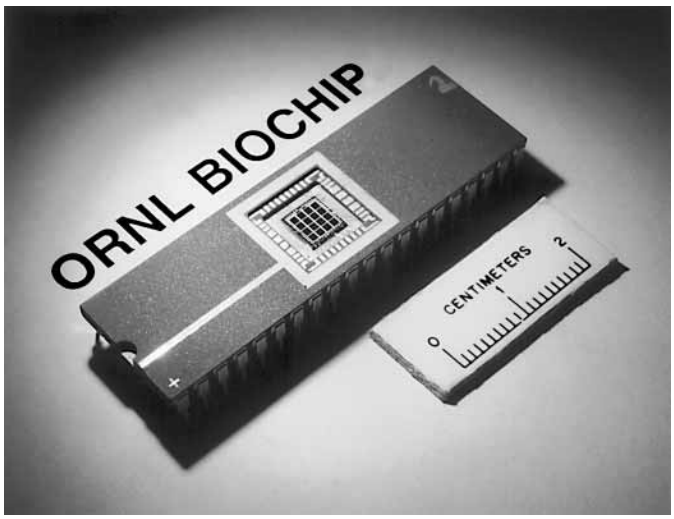

Fig. 5. Photograph of the integrated circuit multiarray system of the DNA biochip.

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Interventional Bronchoscopy beyond the Year 2000

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Gene Therapy for Lung Cancer

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Summary

The lung is a readily accessible target organ for gene therapy, and lung cancer is the second most important pulmonary disease currently treated in phase I and II studies of gene therapy. In the foreseeable future, the best way to achieve reasonable intratumoral concentrations of a transgene with available vectors is injection by bronchoscopy. The focus of this review will therefore be the treatment of lung cancer by bronchoscopic application of gene therapeutic vectors. At present, viral and nonviral methods of gene transfer are used either in vivo or ex vivo/in vitro. The most important viral vectors currently in use in clinical trials comprise retroviruses, adenoviruses, adeno-associated viruses and herpes viruses. None of the available vectors satisfies all the criteria of an ideal gene therapeutic system, and vectors with only minimal residues of their parent viruses ('gutless vectors') as well as completely 'synthetic viral vectors' will gain more and more importance in the future. Nonviral methods of gene therapy include liposomes, injection of vector-free DNA ('naked DNA'), protein-DNA complexes, delivery by 'gene gun', calcium-phosphate precipitation, electroporation and intracellular microinjection of DNA. The first clinical trial of gene therapy for cancer was performed in 1991 in patients with melanoma, and since then, more than 3,500 patients have been treated worldwide in more than 300 clinical protocols. In all these studies, side effects were rare and mostly mild, and expression of the transgene could be demonstrated in patients in vivo. However, despite anecdotal reports of therapeutic responses in some patients, there is still no unequivocal proof of clinical efficacy of any of the different approaches to gene therapy in humans. In addition to our only fragmentary understanding of the molecular pathophysiology of many diseases, the principal reason for the present lack of clinical success of gene therapy is the very low transduction and expression efficiency in vivo of available vectors. Despite the complexities of lung cancer gene therapy, the numerous different approaches can be subdivided into four basic concepts: strengthening of the immune response against a tumor, repair of cell cycle defects caused by losses of tumor suppressor genes or inappropriate activation of oncogenes, suicide gene strategies and inhibition of tumor angiogenesis. In addition, the importance of gene marker studies and the gene therapeutic protection of normal tissue will be covered shortly in this review. Finally, the results of a phase I gene therapy study using an adenovirus carrying wild-type p53 in patients with non-small cell lung cancer carried out at our institution will be discussed in some detail.

The first clinical trial of gene therapy was performed in 1990 in children with adenosine deaminase deficiency, a severe combined immunodeficiency syndrome [1]. Since then, more than 3,500 patients have been treated worldwide in more then 300 clinical protocols. A recurring theme in all these studies was that side effects were rare and mostly mild, and that expression of the transgene could be demonstrated in patients in vivo. However, despite anecdotal reports of therapeutic responses in some patients, there is still no unequivocal proof of

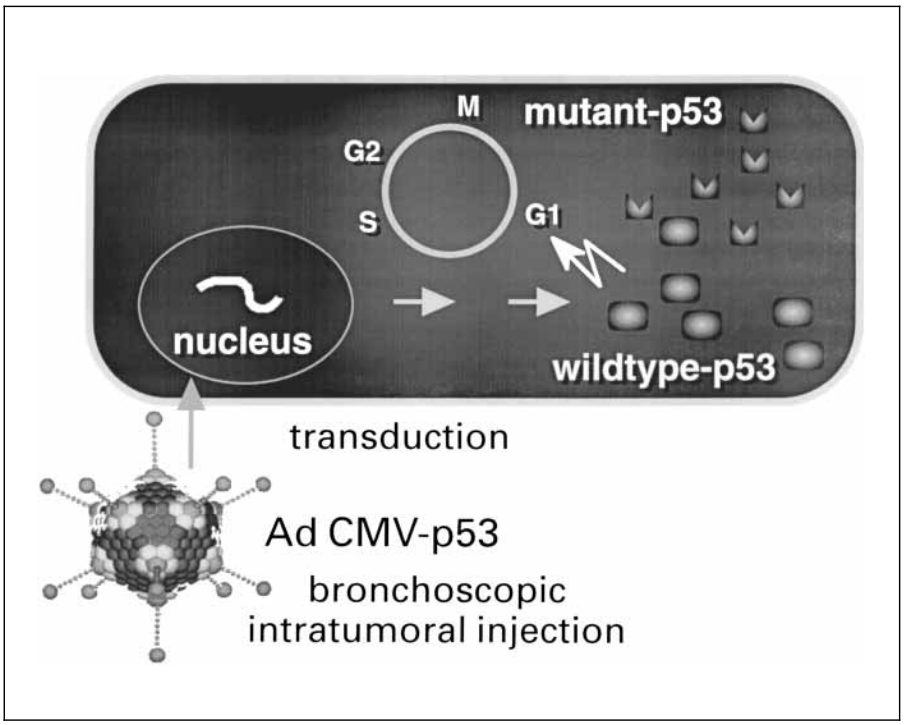


Fig. 1. Transfection of a tumor cell by an adenovirus (Ad) carrying human wild-type p53; expression of p53 is driven by a cytomegalo-virus (CMV) promotor. Wild-type p53 (rectangular symbols) replaces the functions of mutant cellular p53 (cleaved symbols), thus restoring the control of the defect cell cycle (G1-S-G2-M).

clinical efficacy of any of the different approaches to gene therapy in humans [2–7]. In addition to our only fragmentary understanding of the molecular pathophysiology of many diseases, the principal reason for the present lack of clinical success of gene therapy is the very low transduction and expression efficiency in vivo of available vectors.

The lung is a readily accessible target organ for gene therapy. Initially, therapeutic gene delivery had largely focused on introducing functional, corrective genes in lung diseases arising from single gene defects such as cystic fibrosis (CF), α1-antitrypsin deficiency, or surfactant protein B deficiency [8]. More recently, interest has centered on gene therapy as a potential therapeutic tool in modulating complex pathological processes such as pulmonary inflammation, pulmonary hypertension, complications of lung transplantation such as reperfusion injury and graft rejection, and most importantly, lung cancer and malignant mesothelioma [8, 9]. Despite the high expectations associated with the idea of a gene therapy for CF, severe immune reactions against the adenovirus used for gene transfer in the early trials and a disappointingly low transduction rate of pulmonary airway epithelial cells have hampered the further development of this strategy. Nevertheless, encouraging results in animal models and the rapid progress in vector technology justify the hope that within the next decade, a successful gene therapeutic strategy against CF might be available [10].

After CF, lung cancer is the second most important pulmonary disease currently treated in phase I and II studies of gene therapy. In CF, α1-antitrypsin deficiency and most other diseases mentioned above, it should be practicable to apply a therapeutic vector by the inhalation of an aerosol. This is fundamentally different in lung cancer and mesothelioma. Currently, and in the foreseeable future, the only way to achieve reasonable intratumoral concentrations of a transgene with available vectors is injection by bronchoscopy. Therefore, one focus of this review will be the treatment of lung cancer by bronchoscopic application of gene therapeutic vectors.

Methods of Gene Transfer

To eliminate potential risks of gene transfer in vivo, such as induction of malignant transformation or evolution of new viral diseases in humans, the development of vectors with the highest possible safety profile is mandatory. At the same time, the key for eventual future successes of gene therapy is the availability of gene vehicles

Table 1. Methods of gene transfer

Viral vectors
Retrovirus (incl. lentivirus)
Adenovirus
Adeno-associated virus
Herpes viruses
Vaccinia virus
'Gutless vectors'
Completely synthetic 'viral' vectors
Nonviral vectors
Liposomal transfer
'Naked' DNA
Protein-DNA complexes
'Gene gun'
Calcium-phosphate precipitation
Electroporation
Microinjection

with a much better transduction efficiency in vivo than those currently in use in clinical trials.

At present, viral (fig. 1) and nonviral methods of gene transfer are used either in vivo or ex vivo/in vitro (table 1).

Viral Vectors

Approximately two thirds of clinical gene therapy studies carried out so far have used retroviruses as vectors to transfer the foreign gene [2, 3]. The genetic information of retroviruses is coded for by short RNA sequences mainly consisting of initiators of transcription, the so-called long terminal repeats, a signal (ψ) for packaging the RNA into the viral envelope (env), sequences for structural proteins (gag) and for the viral polymerase (pol). Helper cell lines are used to produce retroviral vectors. These cell lines carry a helper retrovirus that is deleted for the ψ sequence and is thus incapable of packaging its RNA into viral particles. The introduction of a genetically modified retroviral vector carrying the transgene instead of 'gag-env-pol' into a helper cell line transforms it into a packaging cell line. Packaging cell lines produce vectors with a viral envelope and structural proteins, but carry the transgene as the only genetic information. Transferred into target cells in vitro or in vivo, the modified retrovirus will then translate the gene of interest but no viral sequences into protein.

The advantages of retroviruses are: (1) their relatively high transfection efficiency; (2) the stable integration of the transferred genetic material into the genome of a target cell, potentially leading to long-term expression of the transgene, and (3) the absence of immunogenic viral proteins in the target cells.

The disadvantages are: (1) the fact that only dividing cells are transducable; (2) the relatively small amount of genetic information (ca. 7.5 kb) that can be packaged into a retrovirus; (3) the uncontrolled integration of the virus into the genome, leading to a theoretical risk of malignant transformation of the affected cells, and (4) the possibility of homologous recombination of therapeutic vectors with endogenous retroviruses resulting in replication of competent new viruses.

Appropriate design of retroviral vectors and helper cell lines allows for a reduction of these risks to a minimum, and in more than 1,000 patients treated with retroviral vectors, neither the induction of a tumor nor the development of replication-competent retroviruses in vivo has been reported [6].

Adenoviruses are the next most important group of vectors used in clinical trials of gene therapy today (fig. 1).

Their advantages are: (1) comparably high viral titers achievable; (2) experience with more than ten million vaccinations with unmodified adenoviruses without major severe side effects; (3) higher packaging capacity compared to retroviruses, and (4) nonreplicating cells are transfectable.

The disadvantages are: (1) the immunogenicity of adenoviruses, making repeated application problematic and (2) no integration into the cellular genome, leading to a loss of genetic information after only a few divisions of transfected cells.

Other viral vectors that are currently used in clinical trials are herpes- and adeno-associated viruses. None of the presently available vectors satisfies all the conditions of an ideal gene therapeutic system. It is likely that vectors with only minimal residues of their parent viruses ('gutless vectors') and completely 'synthetic viral vectors' will gain more and more importance in the future [2].

Nonviral Vectors

Nonviral methods of gene therapy are attractive mainly because they avoid the potential risks inherent to all viral transfer vectors. Liposomes have been used in numerous in vitro and animal studies of gene transfer and are also introduced into the clinic with increasing frequency. Should the main problem of this technique, i.e. the relatively low specificity and efficacy of liposomal transfection be solvable, e.g. by integration of monoclonal antibodies into the liposomal membrane, liposomes ap-

Table 2. Gene transfer and gene therapy in oncology

1	Marker studies
2	Protection of normal tissue
	Transfer of drug resistance genes into bone marrow stem cells
3	Immunopotentiation strategies
	Efficiency of immune effector cells
	Immunogenicity of tumor cells
4	Repair of damaged cell cycle
	Inactivation of oncogenes
	Reactivation of tumor suppressor genes
5	Suicide gene therapy
6	Inhibition of tumor angiogenesis

pear to carry the potential to become one of the preferred methods of gene transfer in future studies [11]. Short-term expression of genes, e.g. during vaccination studies, is achievable with intramuscular injection of vector-free DNA ('naked DNA'), by plasmid DNA coated onto microscopic gold beads that are then delivered using a handheld, helium-driven 'gene gun', and by the use of protein-DNA complexes. Exclusively used ex vivo/in vitro are several physicochemical methods of gene transfer such as calcium-phosphate precipitation, electroporation (introducing pores into the cell membrane by application of electrical voltage) or intracellular microinjection of DNA [2, 3, 11].

Gene Transfer and Gene Therapeutic Concepts in Oncology

Since there are only very few published clinical studies of gene therapy so far, this review will have to focus on currently open protocols and possible strategies of gene therapy in tumor patients. Despite the complexity of the field, the numerous different approaches can be subdivided into four basic concepts: strengthening of the immune response against a tumor, repair of cell cycle defects caused by losses of tumor suppressor genes or inappropriate activation of oncogenes, suicide gene strategies and inhibition of tumor angiogenesis. In addition, we will shortly cover the importance of gene marker studies and the gene therapeutic protection of normal tissue in oncology (table 2).

Marker Studies

The era of clinical gene transfer began in May 1989 with the introduction of an antibiotic drug resistance gene into tumor-infiltrating lymphocytes of patients with melanoma. The procedure turned out to be safe, and expression of the transgene in vivo could be demonstrated for more than 2 months [12].

Marker studies became clinically relevant when several groups showed that in patients undergoing high-dose chemotherapy, peripheral blood and bone marrow cells marked in vitro before retransfusion later contributed to relapse in leukemias and neuroblastoma [13, 14]. These studies proved that the curative potential of high-dose chemotherapy depends not only on the efficacy of drugs given to the patients, but also on better purging methods. In small cell lung cancer (SCLC), numerous trials of high-dose chemotherapy are currently performed, and marker studies similar to those mentioned above have been initiated in almost all tumors treatable by high-dose chemotherapy [4].

Normal Tissue Protection

Although theoretically it is conceivable to transfer genes that protect from the toxicity of chemotherapeutic drugs into many different normal tissues, so far, most experimental and all clinical studies using this approach have targeted precursors of myelopoiesis. Similar to the concept of high-dose chemotherapy with allogeneic or autologous stem cell retransfusion, the goal of these attempts is to increase dose intensity and to simultaneously decrease side effects of conventional cytotoxic drugs. Thus, the transfection of the mdr1 (multiple drug resistance) gene into bone marrow stem cells of mice led to a considerable reduction of paclitaxel-induced myelotoxicity [15]. Interestingly, this effect could be observed only from the second cycle of paclitaxel on, proving an in vivo selection of mdr1-transfected stem cells.

It can be questioned if there is a reasonable chance of a therapeutic breakthrough with this approach in the near future. Reasons for this scepticism are the low transfection efficiency of myelopoietic stem cells with currently available methods (1–10%), the problem of toxicity to other organs when chemotherapy doses are increased, and most importantly, the lack of effective chemotherapeutic drugs in many tumors such as non-small cell lung cancers (NSCLC). Nevertheless, numerous clinical trials using the concept of mdr1 transfer into myelopoietic stem cells have been initiated [4].

Immunopotentiation Strategies

The concept of immunological tumor therapy has been pursued for more than 100 years – without major success for most malignancies. Recently, gene therapeutic ap-

proaches have brought new optimism to the field of tumor immunology, and both immune effector cells and tumor cells have been identified as possible targets of gene transfer.

Improvement in the Efficiency of Immune Effector Cells. The first gene therapy study in oncology transferred the gene coding for tumor necrosis factor (TNF) into tumor-infiltrating lymphocytes to increase their antitumoral activity. With that same goal, a multitude of different cytokines, cytokine receptors, adhesion molecules and 'chimeric antibody/T cell receptor molecules' have been introduced into different immune effector cells in animal models and clinical trials in humans [reviews in 4, 16]. It is currently debatable if, in consideration of the complexity of the antitumoral immune response, the restriction to one transferred cytokine gene and to one type of effector cell can be an effective means to destroy a malignant tumor in vivo [17]. Since several cytokines and cytokine receptors consist of more than one chain, coded for by different genes, an additional problem of this approach is the necessity to express more than one transgene in the same cell, a technique that works especially poorly in human T cells.

Increase in the Immunogenicity of Tumor Cells. Conceptually more convincing are attempts to increase the immunogenicity of tumor cells by the introduction of foreign genes. This approach can potentially work even if neither the immune effector cells involved in tumor cell killing nor tumor-specific antigens potentially recognized by these effector cells are clearly defined – a condition that accurately describes the situation in many immune therapy trials in humans.

The most frequently used approach in animal models consists of the introduction of cytokine genes such as IL-2, IL-4, IL-7, IL-12, INF-γ, TNF-α, or granulocyte/macrophage colony-stimulating factor (GM-CSF) into tumor cells. When injected intratumorally, subcutaneously or by other routes, these manipulated tumor cells are capable of producing high local amounts of the respective protein without causing the usual systemic side effects of cytokines [review in 16]. Since transfection of autologous tumor cells of individual patients is cumbersome and prone to technical problems in clinical trials, and since efficient vectors for in situ transfection are currently not available, many groups have chosen other ways to overcome these restrictions. Allogeneic tumor cells potentially carrying the same specific antigens as the patients' tumors can be transfected with a cytokine gene and then be injected subcutaneously or into the lymphatic system [18]. Alternatively, other autologous, allogeneic or xenogeneic cells such as fibroblasts can be transfected with cytokines, mixed with irradiated tumor cells of the patient and then reinjected into the patient. The common principle of all these studies is the creation of an immunostimulatory paracrine milieu in the close proximity of tumor-specific antigens [19]. In addition to cytokine genes, foreign MHC molecules, viral antigens, known tumor-specific antigens such as the MAGE (melanoma antigen) genes in melanoma, or costimulatory molecules such as B7-1 or B7-2 have been used to increase the immunogenicity of tumor cells in animal models and clinical studies. The different approaches to genetically modify tumor immunogenicity account for approximately two thirds of all gene therapy studies performed in patients with malignancies, and anecdotal evidence of therapeutic success in individual patients has been reported [5]. On the basis of preclinical data and immunological properties of human bronchial carcinomas, cytokines of particular interest for gene therapy in lung cancer include IL-7, IL-12 and GM-CSF [20].

Suicide Gene Therapy

The common principle of sucide gene strategies is the selective intratumoral activation of otherwise nontoxic drugs by specific transfer of the activating transgene into tumor cells. The best known example of such a prodrug activator is the gene coding for the herpes simplex virus thymidine kinase (HSV-TK). As opposed to the human thymidine kinase, HSV-TK phosphorylates the antiherpes drug ganciclovir to toxic triphosphates with very high affinity. In a rat model, stereotactic injection of mouse fibroblasts carrying a retrovirus with an insertion of the HSV-TK gene into gliomas led to a sensibilization of the tumor cells to systemic treatment with ganciclovir and to cure of the gliomas in a majority of treated rats [21]. Clinically interesting in different models of suicide gene therapy was the observation that transfection of only a minority of tumor cells with the prodrug activator gene could be sufficient for a clear benefit of treated animals. This 'bystander effect' was probably due to different mechanisms such as transfer of activated drug via gap junctions between tumor cells, immunological mechanisms after destruction of transfected tumor cells and possibly transfection of endothelial cells of tumor vasculature leading to sensitivity of endothelial cells to ganciclovir and consequently tumor ischemia [21]. Although it is anticipated that similar bystander effects might help to solve the problem of inefficient gene transfer in humans, a recently published study of HSV-TK suicide gene therapy in 15 patients with glioma showed only limited success in

smaller tumors and unconvincing evidence of a bystander effect [22]. Improvements of suicide gene therapy might come with other potentially more effective enzyme-prodrug systems such as cytosine-deaminase/5-fluorocytosine or with an increase in tumor specificity by the use of tumor-specific promotors such as the prostate-specific antigen promotor in prostate cancer or a carcinoembryonal antigen promotor in tumors expressing carcinoembryonal antigen, including many non-small cell and some small cell bronchial carcinomas [7]. Different groups are also currently testing combinations of suicide gene therapy with other gene therapeutic or conventional chemotherapeutic strategies. In mesothelioma, a phase I study has recently been completed using intrapleural injection of an adenovirus expressing HSV-TK in 8 patients. A preliminary report cites low toxicity, evidence for in situ gene transfer and no tumor progression or death during a relatively short observational period [9].

Repair of Damaged Cell Cycle

The development of malignant tumors of the airways is caused by and closely linked to alterations in two groups of genes that are involved in the regulation of the normal cell cyle, oncogenes and tumor suppressor genes. Oncogenes are generally activated by amplification, overexpression, mutation or translocation, and alteration in one allele of an oncogene is usually sufficient to cause cell cycle dysregulation. Deactivation of tumor suppressor genes, on the other hand, occurs by deletion or mutational inactivation, and these molecular alterations are frequently recessive, i.e. both copies of the gene have to be functionally lost for the protein to become inactivated.

Inactivation of Oncogenes. The most important oncogene alterations found in lung cancer concern four genes, RAS, MYC, c-erbB-2, and BCL-2 [23]. RAS is a 21-kd G protein, and up to 30% of bronchial adenocarcinomas show mutations in the K-RAS oncogene that have been associated with poor prognosis. MYC encodes a transcriptional activator and amplification may also adversely affect survival in small cell lung cancer. The growth factor receptor c-erbB-2 is overexpressed in up to 25% of NSCLC cases, and finally, BCL-2, a negative regulator of apoptosis, is expressed differently in some NSCLC [23]. Attempts to reverse the activation of oncogenes in lung cancer have included a preclinical strategy in which a vector encoding for an intracellular single-chain antibody fragment directed against c-erbB-2 has been transfected into tumor cells [9], and a phase I study with antisense K-RAS using a retroviral vector in patients with NSCLC [24].

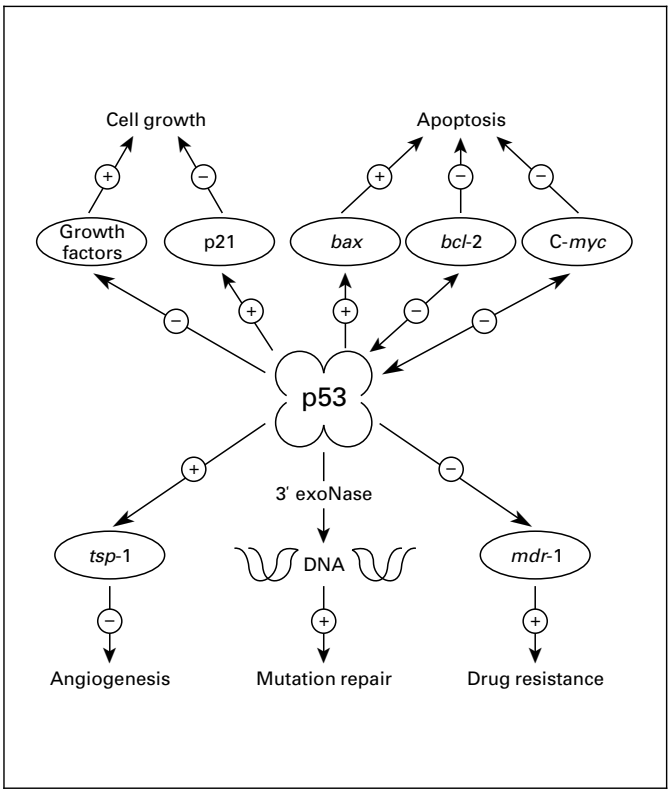
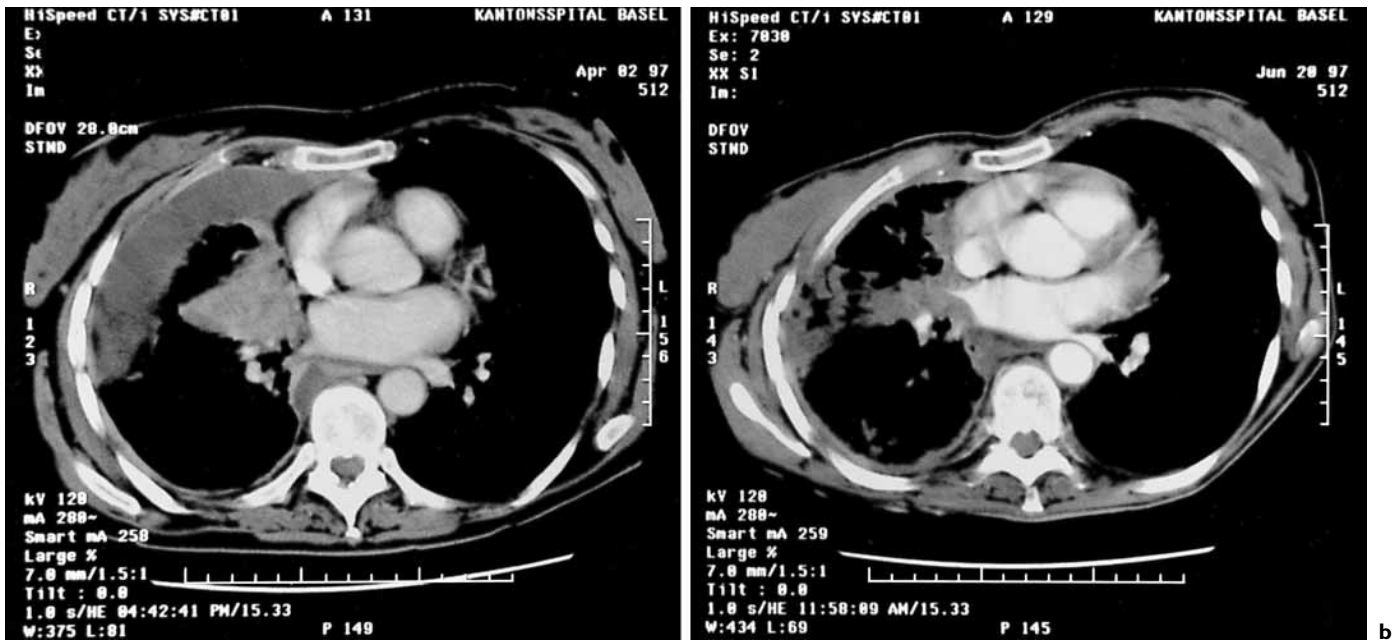


Fig. 2. Wild-type p53 plays a central role in the cell physiology.

Reactivation of Tumor Suppressor Genes. Tumor suppressor genes lost or mutated in lung cancer include the retinoblastoma gene (RB), the gene for the cyclin-dependent kinase inhibitor p16INK4A and the p53 gene [23]. Abnormalities of RB, a key regulator of cell cycle, are detected in more than 90% of SCLCs, and there is an inverse relationship in lung cancer cells between expression of RB and p16INK4A, an upstream regulator of RB. Mutations of p53, with frequencies up to 60% in NSCLC and 80% in SCLC, can lead to loss of tumor suppressor function, increased drug resistance, loss of mutational repair, increased tumor angiogenesis, cellular proliferation and inhibition of apoptosis (fig. 2) [review in 25]. Gene transfer of wild-type p53 was shown to reverse these deficiencies and to induce apoptosis in vitro and in preclinical in vivo tumor models. In light of this preclinical evidence, restoration of functional p53 represents an attractive target for somatic gene therapy in cancer. A pilot study in 9 patients with NSCLC supports this view [26].

Technique and Effects of Endobronchial p53 Application. Based on these results, we initiated a phase I dose



a b

Fig. 3. CT scans of a patient treated with 10^9 PFU of adenovirus-p53 before (**a**) and 2 months after (**b**) therapy. The reduction of the size of the injected lesion fulfills the criteria for a partial remission. The decrease of the volume of pleural effusion is due to a pleurodesis performed directly before gene therapy (courtesy of G. Bongartz, Division of Radiology, Kantonsspital, Basel).

escalation study of a single intratumoral injection of a replication-defective adenoviral expression vector encoding wild-type p53 [27]. Fifteen patients with incurable NSCLC were treated in two centers (University Hospital Mainz, Germany, and Kantonsspital of the University of Basel, Switzerland). All patients enrolled had p53 protein overexpression as a marker of mutant p53 status in pretreatment tumor biopsies. Treatment was performed either by bronchoscopic intratumoral injection or by CT-guided percutaneous intratumoral injection of the vector solution.

Practically, patients were enrolled who had undergone previous bronchoscopies and/or CT scans which had shown that the injection of a volume between 1 and 10 ml of a watery solution was feasible. After informed consent was obtained, the patient then underwent a second fiberoptic bronchoscopy, and 1–10 ml of wild-type p53 containing aquous adenoviral solution was instilled via a 22-G Millrose catheter. Twenty-four hours later, the injected site was biopsied and the tissue examined for wild-type p53 gene expression. Fifteen patients were enrolled, and were treated at four different dose levels ranging from 10^7 to 10^{10} PFU (7.5×10^9 to 7.5×10^{12} particles).

No clinically significant toxicity was observed. Successful transfer of wild-type p53 was achieved with higher vector doses ($\geq 10^8$ PFU). Vector-specific wild-type p53 RNA sequences could be demonstrated in posttreatment biopsies of 6 patients. Transient local disease control by a single intratumoral injection of the vector solution was observed in 4 of those 6 successfully transduced patients. In 1 patient, a clinical response (partial remission $\geq 50\%$ reduction) of the injected lesion was observed 2 months after treatment (fig. 3), but the patient died of progression of noninjected distant metastases. There was no evidence of clinical responses at untreated tumor sites in any patient. In conclusion, wild-type p53 gene therapy by intratumoral injection of a replication-defective adenoviral expression vector was safe, feasible and biologically effective in patients with advanced NSCLC [27].

In a multicenter international study, we are currently testing the combination of repeated injections of 7.5×10^{12} particles of adenovirus-p53 with concurrent platinum-containing standard chemotherapy in patients with NSCLC [unpubl. data]. Figure 4a shows the injection of adenoviral solution using a 22-G Millrose catheter into a right upper lobe lesion in a patient suffering from adeno-

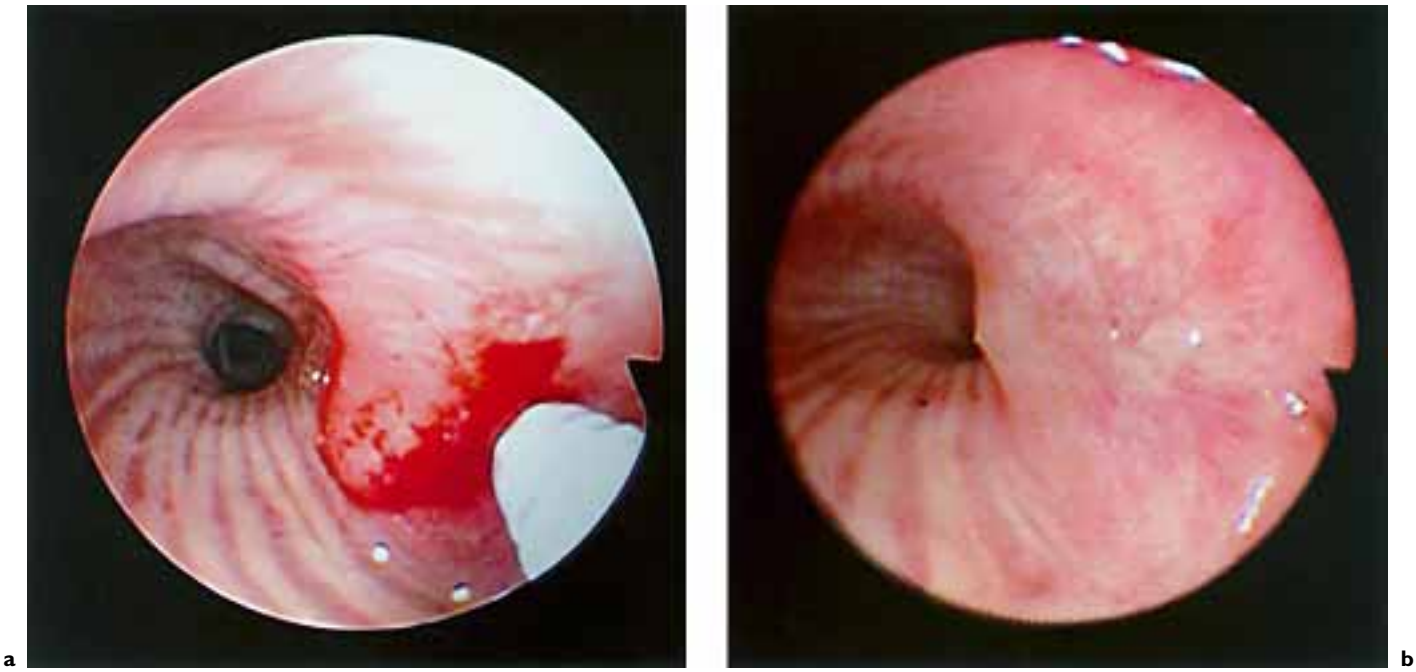


Fig. 4. Bronchoscopy of a patient with an adenocarcinoma of the right upper lobe. **a** Injection of adenoviral solution into a tumorous right upper lobe spur using a 22-G Millrose catheter. **b** The same lesion after three cycles of combined chemo-gene therapy, demonstrating a very good remission of the injected tumor with only scarred tissue remaining in situ (courtesy of A.P. Perruchoud, C.T. Bolliger, Division of Pneumology, Kantonsspital, Basel).

carcinoma; figure 4b shows the same lesion after three cycles of combined chemo-gene therapy, demonstrating a very good remission of the injected tumor with only scarred tissue remaining in situ. Obviously, it is unclear if adenovirus-p53 gene therapy contributed to this response, since chemotherapy alone could have induced tumor shrinkage. On the other hand, adenovirus gene therapy alone has been shown to induce tumor responses by immune-mediated mechanisms in a small phase I study in lung cancer, and randomized trials comparing chemotherapy alone with the combination of chemotherapy and p53 gene therapy are necessary to solve the question if wild-type p53 gene therapy indeed leads to chemosensitization in humans in vivo [28].

An interesting new approach to p53-mediated gene therapy consists of the use of partially replication-competent adenoviruses carrying a loss of the E1B gene region. This loss leads to a selective capability of the virus to replicate in p53-deficient cells, since wild-type adenovirus uses E1B to eliminate the replication-blocking function of cellular p53. Tumor cells with p53 mutations and/or deletions will thus be selectively destroyed by this first example of a new type of tumor-specific vectors [29].

Inhibition of Tumor Angiogenesis

Tumor angiogenesis appears to be crucial for both tumor growth and metastasis in lung cancer as well as in all other solid tumors and, interestingly, also leukemias [30]. Although more than 40 inhibitors of tumor angiogenesis have been tested in clinical studies over the last years without any published major breakthroughs, the field has recently received new attention with the detection of the natural angiogenesis inhibitors endostatin and angiostatin by O'Reilly et al. [31, 32]. The inhibition of angiogenesis seems to be much less hampered by the development of drug resistance than other therapeutic approaches in oncology, since benign endothelial cells which are the target of therapy are genetically stable, homogeneous and have a low mutational rate compared to tumor cells [33]. In bronchial carcinoma, vascular endothelial growth factor, IL-8, tumor growth factor-β, platelet-derived growth factor and basic fibroblast growth factor are important natural angiogenic factors associated with decreased survival in some studies and are targets of anti-angiogenic gene therapy in preclinical cancer models [20].

Conclusion

An evaluation of the first 7 years of gene therapy in 1996 concluded that gene therapy was safe and feasible, but that none of the more than 100 clinical studies performed so far had formally proven the efficacy of the approach in any human disease. The consequence was the request to go 'back to the bench' and develop better viral and non-viral vectors and a better molecular understanding of the pathology of treated diseases [34]. Although anecdotal reports of tumor responses are becoming more frequent in lung cancer and other human malignancies, the situation has not changed dramatically. Main problems are still the lack of vectors with high transduction efficiency in vivo, the low tumor specificity of available systems, the progressive down-regulation of transcription elements in vivo even after successful transfer of a transgene, and our incomplete knowledge of molecular tumor pathology.

However, the results of the few published phase I studies of gene therapy in lung cancer [8, 9, 20, 26–28] are encouraging, and important progress in vector technology is expected in the near future. It is likely that tumor-specific vectors and tissue-specific promotors will be in routine use within the next 5–10 years, and that the completion of the human genome project will lead to major advances in our understanding of the molecular aspects of carcinogenesis, tumor progression and metastasis [2]. The first intravenously applicable vectors should be available at the end of this period and expression of a transgene in a sufficient percentage of targeted tumor cells achievable. The most likely scenario of the role of genetic approaches to the treatment of lung cancer during the next two decades will be a modest contribution within a multimodality treatment concept consisting of surgery, radiotherapy, chemotherapy, endoscopic treatment modalities and – hopefully – immunotherapy and gene therapy.

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Author Index

Subject Index