Thoracic Endoscopy: Advances in Interventional Pulmonology

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This volume would not be complete if we did not thank our mentors, teachers, colleagues and friends. The insight, support and guidance of these individuals have facilitated both the genesis and the metamorphosis of this emerging discipline of interventional pulmonology. For those of us who look toward the future it is wonderful to have support and experience to rely on for this journey into the future and company along the way. Thank you all.

— Editors

To my past, future and present: my past, my parents, James and Ilinka, who have given me the foundation to achieve that which I strive toward. My future, my son Evan, who has reopened my eyes to the many whys around us. My present, my wife Evonne, whose love, support and guidance I could not do without, each and every day of my life; with her at my side I will always be successful.

— Michael J. Simoff

To my wife, Jamine, for her patience and support,
To my children, Drew, Grant and Caroline, for their love and spirit,
And, to my parents, for their inspiration.
Without all of you, none of this would have been accomplished.

— Daniel H. Sterman

I dedicate this work to my wife Dayna, whose never ending support is what makes efforts like the publication of this book possible.

— Armin Ernst

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Blackwell Futura is an imprint of Blackwell Publishing

Blackwell Publishing, Inc., 350 Main Street, Malden, Massachusetts 02148-5020, USA
Blackwell Publishing Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK
Blackwell Science Asia Pty Ltd, 550 Swanston Street, Carlton, Victoria 3053, Australia

First published 2006

1 2006

ISBN-13: 978-1-4051-2204-7
ISBN-10: 1-4051-2204-8

Library of Congress Cataloging-in-Publication Data

Thoracic endoscopy : advances in interventional pulmonology / edited by Michael J. Simoff, Daniel H. Sterman, Armin Ernst.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-4051-2204-7 (alk. paper)
ISBN-10: 1-4051-2204-8 (alk. paper)
1. Chest–Endoscopic surgery. I. Simoff, Michael J. II. Sterman, Daniel H. III. Ernst, Armin.
[DNLM: 1. Lung Diseases–surgery–Case Reports. 2. Bronchial Diseases–surgery–Case Reports. 3. Bronchoscopy–methods–Case Reports. 4. Pleural Diseases–surgery–Case Reports. 5. Thoraco-scopy–methods–Case Reports. WF 668 T487 2006]

RD536.T454 2006
617.5′407545–dc22

2006006133

A catalogue record for this title is available from the British Library

Acquisitions: Steve Korn and Gina Almond
Production: Simone Dudziak and Beckie Brand

Set in 9.5/12 Minion by Newgen Imaging Systems (P) Ltd., Chennai, India
Printed and bound in Harayana, India by Replika Press PVT Ltd.

For further information on Blackwell Publishing, visit our website:
www.blackwellpublishing.com

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Foreword

The centennial anniversary of bronchoscopy is now several years behind us. The modern era of interventional pulmonology is more than two decades old. However, many decades ago and before the advent of the flexible bronchoscope, some physicians (usually surgeons) resected some tumors with rigid bronchoscopes and forceps. Moreover, thoracoscopy was first performed in 1910 by an internist who used a cystoscope to explore the pleural space [1]. It is tempting to consider myself as an interventional pulmonologist who began his work at the advent of interventional pulmonology, but clearly this is not so. However, the progress of instrumentation and techniques since the 1980s force me to reflect that what we did in the early 1980s was very pedestrian. In the current era, new instruments have been developed and innovative thinking has made interventional pulmonology more widely available. There is crossover of practice, such that many interventional pulmonologists have expanded their practices to include forms of care that were once done almost exclusively by surgeons.

This book is written by many of the pulmonologists and surgeons who practice interventional pulmonology as a major part of their professional activities. For it to be used and understood as an up-to-date and excellent reference, the reader should have solid foundations and an understanding of basic diagnostic bronchoscopy and simple procedures that are part of the practice of chest medicine.

The editors have developed three complementary sections of the book, beginning with advanced diagnostic bronchology. In the first chapter, a method for detecting occult malignancies (autofluorescence bronchoscopy) is explained in detail. This was strictly a research method until very recently. Another emerging field that has great promise for diagnosis and staging is endobronchial ultrasound. The potential to improve patient care is truly impressive. Other advanced diagnostic techniques and use of simulators round out the first section of the book.

In the second section the editors have clustered the latest skills for interventional bronchoscopy. Rigid bronchoscopy, I am happy to see, occupies the leadoff position. I still believe that an interventional pulmonology service is incomplete if the physician does not acquire the requisite skills to use a rigid bronchoscope well. A variety of ablative instruments are described for use with bronchoscopes, and the costs and advantages of one or the other instrument are compared. Stents are now available in many sizes, shapes and materials. None is perfect, but the choice among the many options is explained to the reader. The future potential for endobronchial lung reduction therapy and gene therapy with the bronchoscope are discussed.

Next, the editors provide a window to the pleura with a variety of topics that typically take additional training beyond the years of standard residency and fellowship programs. Finally, a series of illustrative cases are presented with excellent photographs to enhance the application of these techniques in a given practice.

Not all interventional pulmonologists will choose to master each of the practice patterns that are described, but this book provides a concentrated and cohesive orientation to all that is available to such physicians at the moment. The editors are among the most highly recognized names in the field today, and they are continuing to provide advances for the rest of us to incorporate into our practices. I extend my thanks to each of them and their contributing authors for a collection

that should serve as a ready reference for the student and the more experienced interventional pulmonologist alike.

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Reference

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Preface

As the title of our textbook implies, the field of interventional pulmonology has expanded beyond just managing malignant diseases of the trachea and mainstem bronchi to the diagnosis and management of diseases of the entire thorax. We felt that the title of the text, 'Thoracic Endoscopy' more completely encompasses the expansiveness of the field of interventional pulmonology, which we continue to practice and hope to continue to expand.

From the inception of the practice of interventional pulmonology, there has been enthusiasm for the practice of therapeutic procedures; from the initial use of lasers and the 'rediscovery' of the rigid bronchoscope to electromagnetic guided bronchoscopy and endobronchial lung volume reduction. As the field grows, the breadth and depth of our contribution to the diagnosis and management of diseases of the chest will also continue to grow.

In regard to chest malignancies, the further advancements of endobronchial ultrasound, autofluorescence and optical coherence tomography as well as external navigational techniques will provide for a more comprehensive diagnostic armamentarium to identify and stage diseases. With advances in laser, electrosurgical and the evolution of tracheobronchial stenting, interventional pulmonology can treat endobronchial disease better than before. With advancements in medical thoracoscopic procedures, we have expanded our expertise to diagnosis, monitoring and treatment of the pleural space.

Benign tracheobronchial diseases are now a regular part of the interventionalist's realm, for both diagnosis as well as treatment. This not only includes diseases of the large airways such as tracheal stenosis or tracheobronchomalacia, but also diseases of the small airways – emphysema and asthma. Advancements in percutaneous tracheostomy and other related procedures have served to expand the diversity of our contribution to management of the critically ill patient.

Interventional pulmonology will only continue to grow as a specialty, particularly as the field incorporates advances in nanotechnology and molecular medicine. The technologies that exist on the horizon are exciting and awesome. This textbook is merely an outline to the myriad of possibilities available to the inventive and far-reaching mind of the advanced chest endoscopist.

Michael J. Simoff, MD
Armin Ernst, MD
Daniel Sterman, MD

PART I

Advances in diagnostic bronchology

CHAPTER 1

Autofluorescence in the detection of lung cancer

Michael J. Simoff, MD

Perception depends upon the detection technique. What we see is the result of the brilliant possibilities of the human eye and human brain.

Martin Leonhard, "New Incoherent Autofluorescence/Fluorescence system for Early Detection of Lung Cancer"

Lung cancer continues to be the leading killer among all cancers. Despite recent advancements in treatment, the 5-year survival rate for lung cancer remains at approximately 15%. In the 25% of patients diagnosed with lung cancer who are offered surgery for curative resection, only one half are ultimately cured of their disease. The greatest hope for patients is the early detection of lung cancer allowing them the opportunity to attempt a treatment course for a cure.

These poor statistics do not reflect on the aggressiveness of treatment, rather on the late diagnosis and frequent recurrence of lung cancer in patients. Finding a solution to the dilemma of how to diagnose lung cancer early remains a goal of many researchers. Chest radiographs and computed tomography screening [1–3] have been and are being looked at to identify this disease earlier in its development.

With only 30% of early endobronchial cancer and/or premalignant lesions identified by white light bronchoscopy (WLB) [4], it would be an understatement to say that we are missing many opportunities for the treatment of early synchronous and metachronous tumors. What is needed is a new modality to detect early forms of the disease, which then have the opportunity to be aggressively treated and potentially cured, some with endobronchial techniques. One such technology for early detection is autofluorescence bronchoscopy (AF).

Autofluorescence is not the answer to the dilemma of the diagnosis of lung cancer, but it may give us another tool for not only diagnosing, but also guiding management decisions [5], thus better allowing us treatment planning and option evaluation for patients with lung cancer. The format of this chapter will be to guide the reader through the whys and hows of AF bronchoscopy prior to discussing the actual clinical use. Only by understanding what information we gain by AF can this tool be effectively used.

The problem

Despite advancements in chemotherapeutic agents, radiation and surgical techniques, the recurrence rate of lung cancer is 3.6–4% per year. Second primaries occur in 17% of patients within 3 years of treatment of their primary disease [6,7]. With 10–20% of patients having a second primary or recurrence, it suggests a more complicated process than a single tumor alone.

The presence of synchronous primary cancers is common. Of the patients who die of lung cancer, 15% have synchronous carcinoma in situ (CIS), with a prevalence of 3.4% among one–two packs per day smokers, and 11.4% among patients smoking greater than two packs per day [8]. Qu *et al.* [9] looked at 225 subjects, including patients with known or suspected lung cancer, patients post

Table 1.1 Comparison of patients with known or suspected lung cancer. Status: post resection for lung cancer, with head and neck cancer and healthy volunteers for the presence of precancerous and cancerous lesions [9].

Group	*n*	*Moderate dysplasia* (%)	*Severe dysplasia* (%)	*CIS (%)*	*≥2 foci (%)*
I	100	14	11	15	15
II	46	18	4	13	24
III	10	20	10	10	20
IV	67	36	15	5	13

n, number of patients.
I, known or suspected lung cancer.
II, stage I completely resected lung cancer.
III, head and neck cancer.
IV, volunteer smokers.

complete resection for lung cancer, those with head and neck cancer and in healthy volunteer smokers (Table 1.1). In the group suspected of cancer, 25% had moderate to severe dysplasia and 15% had CIS, with 15% of these patients having greater than two foci. In the postoperative group 22% of patients were identified to have dysplasia and 13% with CIS, 24% of which had multiple foci. The patients with head and neck cancer had a 30% prevalence of dysplasia and 10% of CIS, 20% multifocal. And last, the volunteer smokers included 51% with dysplasia and 5% with CIS, 13% of which had greater than two foci.

Carcinogenesis

> The concept of carcinogenesis is a multi-step process, suggesting the possibility of blocking or reversing the progression and thus presents the opportunities for a more effective intervention.
>
> Vogelstein *et al.*,
> "The Multistep Nature of Cancer"

The pattern of multifocal areas of dysplasia and CIS in many ways supports the theory of field cancerization as it applies to cancer of the aerodigestive tract [10]. As they are inhaled, cigarette smoke and/or other irritants thought to be the primary carcinogens for lung cancer, expose the entire aerodigestive tract to potential injury. This diffuse injury to the mucosa of the lung should probably be expected rather than be surprising to us. The initial changes of genomic instability within a morphologically normal epithelium begin the molecular stage of carcinogenesis [9]. These mutation-induced changes could therefore be expected to occur throughout the respiratory epithelium.

The process of carcinogenesis begins with the initial injury to the endobronchial epithelium. The genetic mutations that occur in response to this injury bring about the morphologic findings identified as premalignant changes in the tissue. This process of mutagenesis, from normal tissue through metaplasia and subsequently dysplasia, takes 3–4 years to occur usually [11–14]. Once identified, endobronchial dysplasia is a difficult problem in that it is unclear as to the evolution of disease from this stage of change. There can be an apparent resolution of dysplasia to morphologically normal tissue that has been identified and reported [15]. The gradation of mild and moderate to severe dysplasia have progressively stronger implications of areas of true concern, regarding the development of cancer. The pathologic evolution from severe dysplasia to CIS takes about 6 months [11]. Therefore, from the time of a tissue injury, which induces the pathologic changes that allows the development of a cancer, multiple other areas throughout the epithelium have sustained similar injury and must be at similar risk for the development of cancer.

Several authors have studied the rate of progression from CIS to microinvasive cancer; one group demonstrated a 23% progression rate of CIS to microinvasive cancer, by performing follow-up bronchoscopies every 3 months [15]. Venmans *et al.* [16] followed pathologically confirmed CIS in their patients every 3–4 months with bronchoscopy also. They eventually confirmed that all but one of their patients developed an invasive carcinoma of the airways, which required therapy. The single individual in whom CIS did not evolve into a microinvasive cancer in the study had enough macroscopic changes by WLB alone; hence, therapy was begun despite incomplete evolution of the pathologic changes.

Overall, several authors have also begun to look at the issue of progression of endobronchial pathology. It is suggested by review of data available that 10% of moderate dysplasias, 19–46% of severe dysplasias and 22–56% of CIS will eventually evolve

from their current state to an invasive cancer [15–19].

As is suggested here, not all lesions progress to a more evolved state of disease; some actually spontaneously regress or demonstrate no histologic change over time. The studies available, which have used sequential surveillance bronchoscopy with AF, have all had limited numbers of patients [14,16,20,21]. In two of the studies, precancerous lesions that persisted for 3–6 months were treated with endobronchial modalities limiting the length of follow-up [16,20]. Lam *et al.* did follow endobronchial changes with AF in 17 patients with pre-invasive disease for up to 4 years. Of these patients 5 progressed to an invasive squamous cell carcinoma. The lesions in the remaining 12 patients, on the other hand, remained in a pre-invasive state throughout the 4-year follow-up [21]. Unfortunately, despite the knowledge that some lesions improve with time, we are left in a situation where we do not know, nor do we have the capacity at this time to differentiate, which lesions will progress, stay the same or remiss to normal mucosa. AF gives us new information on the identification of these lesions, but also added questions as to what to do with them.

Microscopic anatomy of the airways

The airway is a multilayered structure, consisting of the ciliated epithelium (46 ± 3 microns) with the underlying basement membrane. Immediately below the basement membrane is the submucosa (680 ± 20 microns), which consists of mucous glands, collagen, elastin, nerves, lymphatics, and vascular structures. Smooth muscle separates the submucosa from the cartilaginous layer (1.2 ± 0.1 mm) of the airway. The adventitia, a connective tissue sheath containing branches of bronchial arteries and veins and nerve plexi, is the outer most layer of the airway [9,22].

The pathologic changes of dysplasia, CIS and microinvasive carcinoma are very superficial. These changes occur initially in the epithelium, eventually invading through the basement membrane and into the upper submucosa (Figure 1.1). Pathologic evolution of microinvasive cancer usually involves the superficial 70–116 microns of the airway [9].

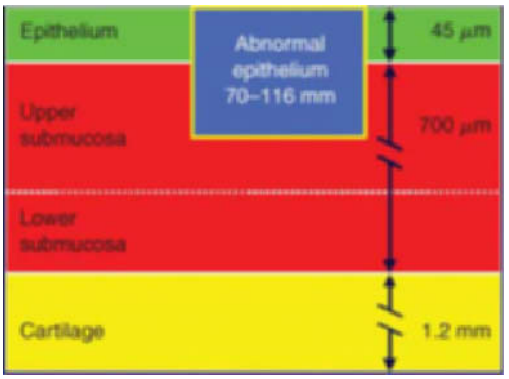

Figure 1.1 Depth of penetration of early cancerous lesions in respect to microscopic anatomy of the bronchus wall.

It is important to understand the process of carcinogenesis as well as the microscopic anatomy of the airway to effectively use the technique of AF.

WLB and the detection of early disease

Due to the intra-epithelial to superficial submucosal development of CIS and microinvasive cancers, it is difficult to diagnose many of these sites with conventional WLB techniques alone. CIS and early cancers are only detected with WLB about 29–40% of the time [4,7,23–25]. This is due to the fact that these early pathologic lesions are only a few cells thick (0.2–1 mm) leading to only minimal mucosal changes. When visualized, these precancerous and early cancerous lesions are superficial, often flat lesions, which are usually less than 5 mm^2 in surface area. Endobronchial changes less than 10 mm^2 are commonly invisible to standard WLB observation. With WLB, many of these lesions present as nonspecific changes of the endothelium such as a pale or a more reddish discoloration of the mucosa. Other epithelial changes observed by WLB examination include a lack of luster or a rough/microgranular appearance of the mucosa [23,25,26]. Mucosal folds and bronchial bifurcations can be swollen or thickened with nodular lesions becoming more evident after they have grown greater than 2 mm in size [23,25].

Bronchoscopic evaluation of the airways can take place in bronchi of the fifth order with modern flexible WLB [27]. As the clarity of images continues to improve with the advancement of bronchoscopic

optics, what will be the role for AF bronchoscopy? I was challenged on one occasion with this very question. The questioner explained that with his newest generation bronchoscope, he could see the vascularity of the bronchial mucosa with great clarity; why then, with such advanced optics, do we need a different tool to look for subtle endobronchial changes when they should be clearly visible. My response was simply: "So do you look?" The changes we are trying to identify are subtle. Having the capability to examine the airway and actually performing such a detailed examination in a breathing, coughing patient is very different. The technology used for AF allows us an improved ability to look for subtle changes throughout the airways of our patients in a relatively straightforward, safe and effective manner.

There have been multiple studies attempting to use conventional WLB to identify early stage lung cancer. One such study used WLB to evaluate the airways of patients with positive sputum cytology for lung cancer. They identified CIS or microinvasive cancer in 61% of patients who were examined, making the diagnosis of an early cancer in 88% of the patients (44 of 55 patients) [28]. Sato and colleagues [29], looked at 180 patients who underwent 527 bronchoscopies. Two hundred occult cancers were identified during the time of the study. To achieve this result though, it required a mean of 29.2 months and an average of three bronchoscopies for each patient to attain a definitive diagnosis. Both groups of investigators identified early stage cancers; the limitations in time to diagnosis and the number of bronchoscopies required make this approach of limited value and less practical for clinical application.

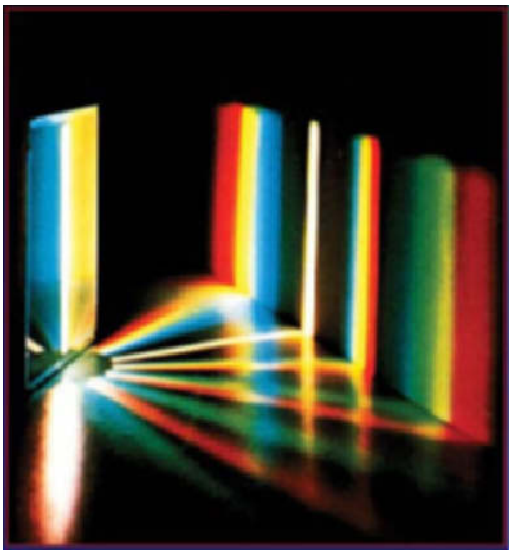

Figure 1.2 White light separated into various wavelengths (colors) through a prism. (Image courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

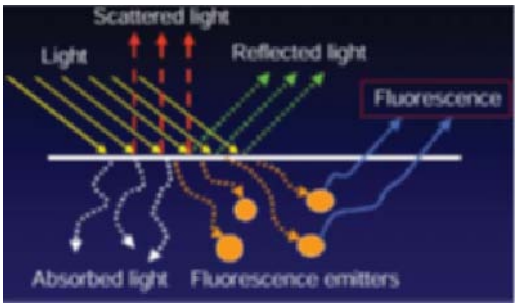

Figure 1.3 Reflectance imaging: the four physical properties of light as it interacts with a surface: absorption, scattering, reflection and fluorescence.

Light

Light is a form of electromagnetic radiation. White light, as in sunlight or incandescent light, is a polychromatic blend of all wavelengths of the spectrum of visible light. White light can be separated into individual wavelengths; each distinct color can be exposed by passing the white light through a prism or as is similarly seen in a rainbow (Figure 1.2). We see in color due to the various light wavelengths and their interactions with objects and/or tissue.

When white light is shown onto a surface, and for the purpose of this discussion, specifically a tissue surface, the colors that we see are due to several of the physical properties of light: scattering, absorption, reflection and fluorescence. (Refer to Figure 1.3 for the following discussion.) As light strikes a surface, some of the light is scattered in different directions still as white light. Our observation of this phenomenon is often referred to as glare. As the same light strikes a surface, some wavelengths of light are absorbed into the tissue/structure. These wavelengths of light are absorbed into various

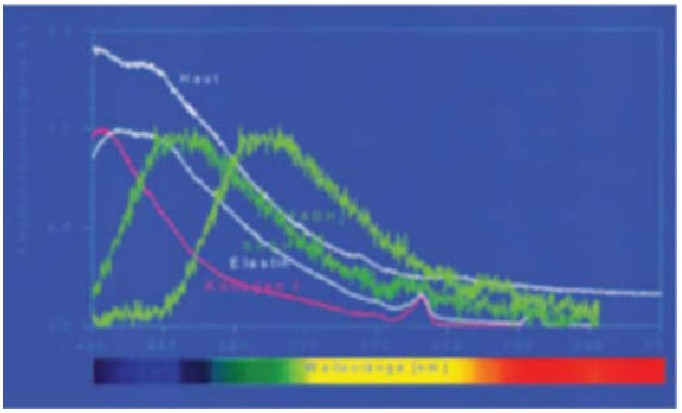

Figure 1.4 Florescence wavelengths of the major tissue fluorophores: $FADH_2$, NADH, elastin and collagen 1. (Image courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

components of the structure (cells, molecules, etc.). This absorption leads to loss of these wavelengths of light. The remaining light wavelengths that are reflected off the tissue/structure surface are blended into the colors that we see objects in. This combination of effects of reflection, back scattering and absorption are known as reflectance imaging. We observe by reflectance imaging when using WLB.

Autofluorescence

As white light strikes a tissue surface, and reflectance imaging occurs, as mentioned earlier, some of the light is absorbed. Certain cells within the epithelium and upper submucosa, known as fluorophores, are stimulated by this influx of energy (Figure 1.1). The most commonly recognized fluorophores in the epithelium and submucosa are collagen I and II, elastin, NADH and $FADH_2$ (Figure 1.4). Fluorophores absorb short wavelengths of light, usually about 390–460 nm (blue light), stimulating electrons from their ground state energy level (E1) to an excited state (E2). Spontaneous decay from the excited state leads to the emission of longer wavelengths of light from the fluorophores that are eventually released from the surface of the tissue (Figure 1.5). These higher wavelengths of light that are released are of 520 nm, which is seen as green, and of 630 nm, seen as red (see Figure 1.6).

Fluorescence or AF is expressed by all tissue surfaces stimulated with white light, or more specifically the shorter wavelength blue light (390–460 nm) within white light. AF is always present, but as it is 10 000 times dimmer than reflected light, it is not visualized with normal viewing. The tissue epithelium is not very biologically active and is responsible for less than 5% of tissue released AF. On the other hand, due to their cellular makeup, the submucosa and cartilage have strong AF potentials. Due to the shallow penetration of blue light into the tissue surface, clinically observed AF is a characteristic of the upper submucosa predominantly (Figure 1.1) [30,31].

The tissue characteristic of AF was first discussed in the literature in 1933 [32]. Historically, AF was pharmacologically augmented by the use of photosensitizers like partially purified hematoporphyrin. With further advancements in 1961, hematoporphyrin was found to have preferential retention in cancer cells [33]. In 1979, hematoporphyrin was used in work pertaining to the early detection of lung cancer by Doiron *et al.* [34]. As our knowledge of photobiology progressed, new pharmacologic agents were developed including hematoporphyrin II in 1979 [35]. Low doses of hematoporphyrin II were used by Palcic *et al.* to clinically identify early stage lung cancer [36].

The next leap in technology was in 1990 with the development of a Lung Imaging Fluorescence Endoscope (LIFE) (Xillix Technologies Corp., Richmond, British Columbia, Canada). LIFE bypassed the need of photosensitizers, rather using low energy monochromatic laser light to stimulate cellular AF. A series of filters and cameras were then used to allow clear visualization of the green and red light generated by AF [37].

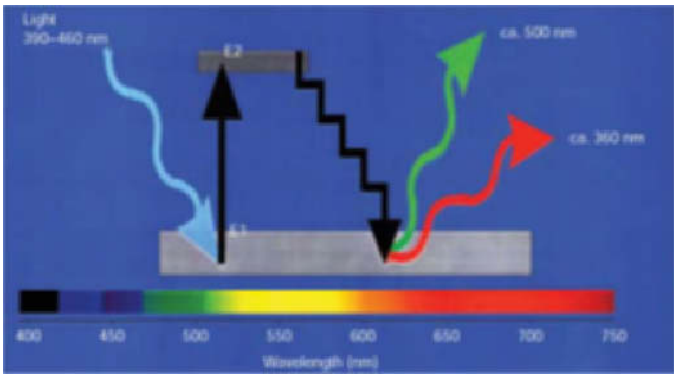

Figure 1.5 Certain wavelengths of light (390–460 nm) excite molecules in fluorophores to higher energy states (E2). Spontaneous decay produces fluorescence with emittance of green (520 nm) and red (630 nm) light. (Image courtesy of Karl Storz of America, Culver City, California USA, with permission.)

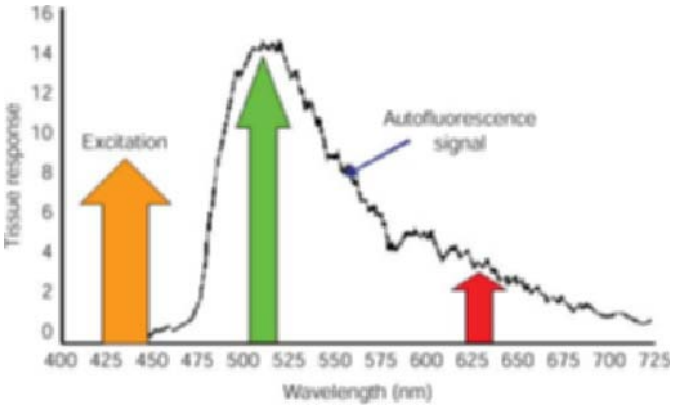

Figure 1.6 Relative release of green and red wavelengths of normal tissue in response to excitation. (Image courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

Autofluorescence bronchoscopy is performed by the stimulation of fluorophores by illuminating them with a monochromatic light source (helium–cadmium laser, filtered xenon or metal halide light sources). Reflectance is then filtered out and with the assistance of filters and specific optical camera systems images in green and red are visualized. With AF normal bronchial epithelium is visualized in green (520 nm), due to the predominate formation of these wavelengths of green light by normal stimulated fluorophores. Areas of the submucosa or epithelial layers that have precancerous changes or have evolved into microinvasive cancers will have a diminishment in the green light released and subsequently increased visibility of red light (630 nm) produced.

The reduction of visualized green light is due to the pathologic changes associated with the cellular evolution into a microinvasive cancer. An early change in the process is thickening of the epithelium, which allows less of the delivered light to pass into the submucosa, overall decreasing the AF that is produced. Second, cancer-induced angiogenesis occurs within the thickened epithelium and upper submucosa as the cancer continues to grow locally. Blood is visualized by the naked eye as red, due to the fact that blood products have an increased absorption of colors other than red, in this case green, leaving red as the predominate color visualized. Thereby the localized angiogenesis of cancer formation increases the red as seen with AF. The pathologic formation of a cancer also includes changes to the extracellular matrix in the epithelium and submucosa by secretion of mefalboproteinase by proliferating cancer cells. These structural changes in the submucosa also reduce the AF produced, but more significantly reduce the green produced from affected areas (Figures 1.7a–c and 1.8) [29,38,39].

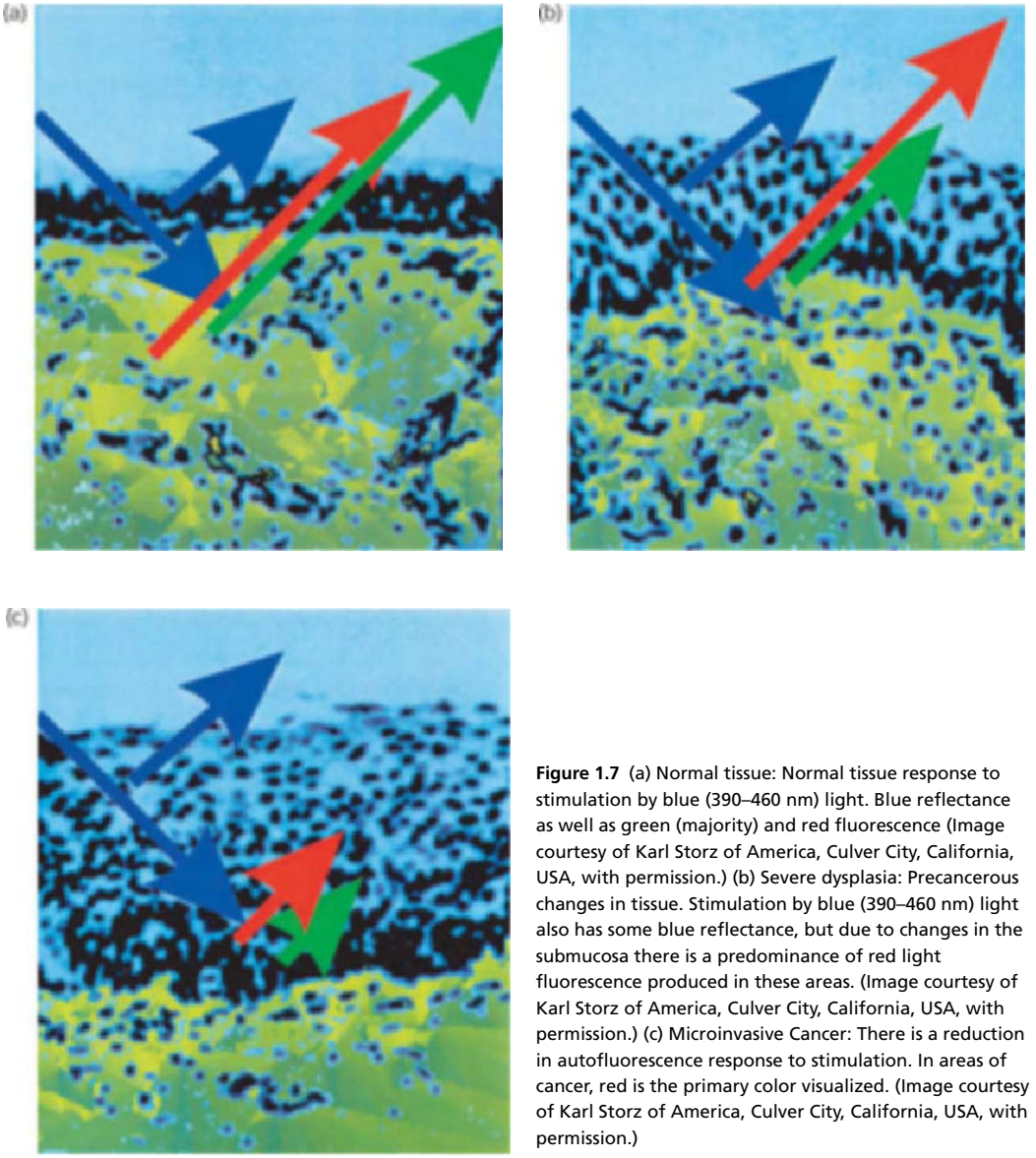

Figure 1.7 (a) Normal tissue: Normal tissue response to stimulation by blue (390–460 nm) light. Blue reflectance as well as green (majority) and red fluorescence (Image courtesy of Karl Storz of America, Culver City, California, USA, with permission.) (b) Severe dysplasia: Precancerous changes in tissue. Stimulation by blue (390–460 nm) light also has some blue reflectance, but due to changes in the submucosa there is a predominance of red light fluorescence produced in these areas. (Image courtesy of Karl Storz of America, Culver City, California, USA, with permission.) (c) Microinvasive Cancer: There is a reduction in autofluorescence response to stimulation. In areas of cancer, red is the primary color visualized. (Image courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

Figures 1.9–1.12 are examples of side-by-side views of the airway with WLB and AF in a normal trachea, with epithelial changes of dysplasia, *CIS* and a microinvasive carcinoma. (The AF images were created by the Storz D-Light system.)

The technology

The initially developed and still commonly used tool for AF bronchoscopy is Laser Induced Fluorescence Endoscopy or LIFE system (Xillix Technologies Corp., Richmond, British Columbia, Canada). The LIFE system uses a low-energy helium–cadmium laser at a wavelength of 442 nm for fluorophore stimulation. Two charge coupled device (CCD) cameras connected through a fluorescence collection sensor and optical multi-channel analyzer are used via an optical bronchoscope. The image is then processed through an image board, which transforms the various light

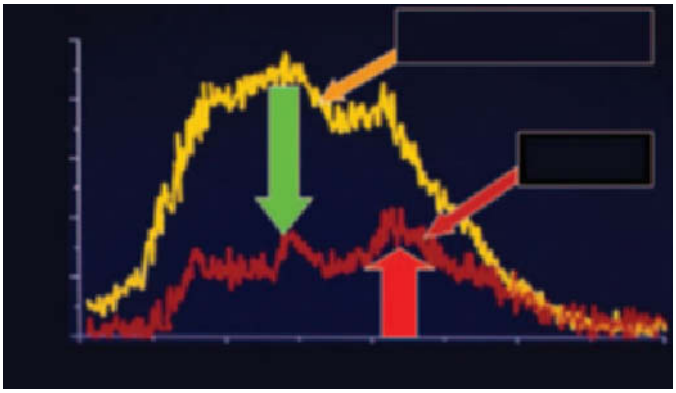

Figure 1.8 Wavelength production by autofluorescence for both normal tissue and areas of the tumor. The relative reduction in green wavelength production is clearly identified. (Image courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

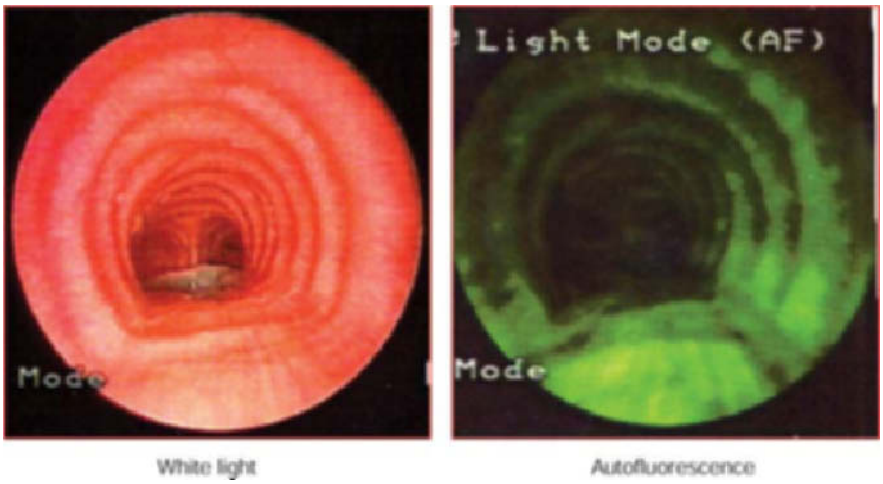

Figure 1.9 Normal Tissue: View of trachea with white light and AF light sources. (Image produced with D-Light system, courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

intensities into a real time video image augmenting the green of normal tissue and the red of abnormal tissue (Figure 1.13a,b).

The D-Light system (Karl Storz Endoscopy of America, Culver City, California, USA) uses a xenon light source. The white light produced by the xenon light source is transmitted to a dedicated optical bronchoscope through a liquid light cable. A series of filters are fit into the eyepiece of the bronchoscope, which generates the monochromatic light needed (380–460 nm) for fluorophore stimulation. Additional filters are used to reduce reflectance of the blue light from the tissue allowing only red and green wavelengths to be visualized. The resulting image is seen in green (normal tissue) and red (tissue with pathologic changes). Due to the faint nature of tissue AF a reduced imaging speed (16 images per second versus 60 images per second in normal WLB) is currently used with the D-Light system to enhance light absorption and therefore clarity of the image of the abnormal tissue. The system has a footswitch and switch on the attached camera to allow quick changes from white light to AF modes , thus permitting the operator to choose which light source best fits his or her needs at any time during the examination (Figure 1.14; see Figures 1.9–1.12 for images).

The Diagnostic AutoFluorescence Endoscopy (DAFE) (Richard Wolf Endoskope, Knittlingen, Germany) is another technology using a filtered

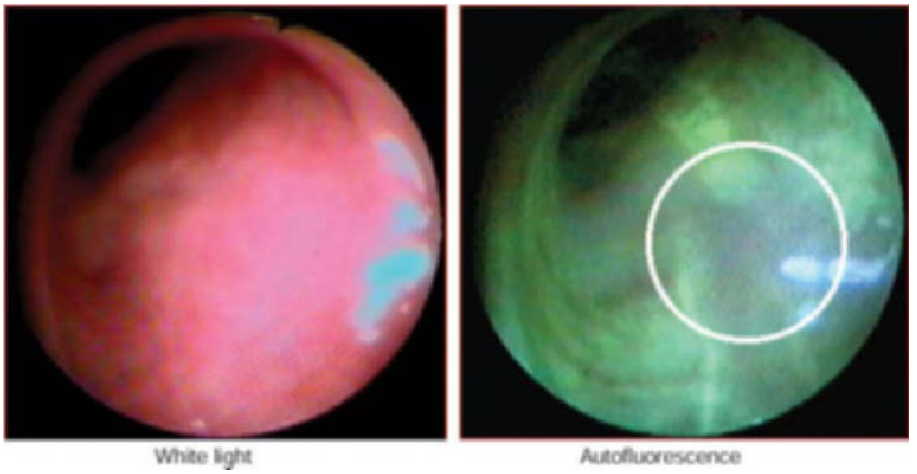

Figure 1.10 Dysplasia: White light and autofluorescence localization of dysplastic tissue. Green identifies normal tissue and red identifies abnormal, precancerous tissue. (Image produced with D-Light system, courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

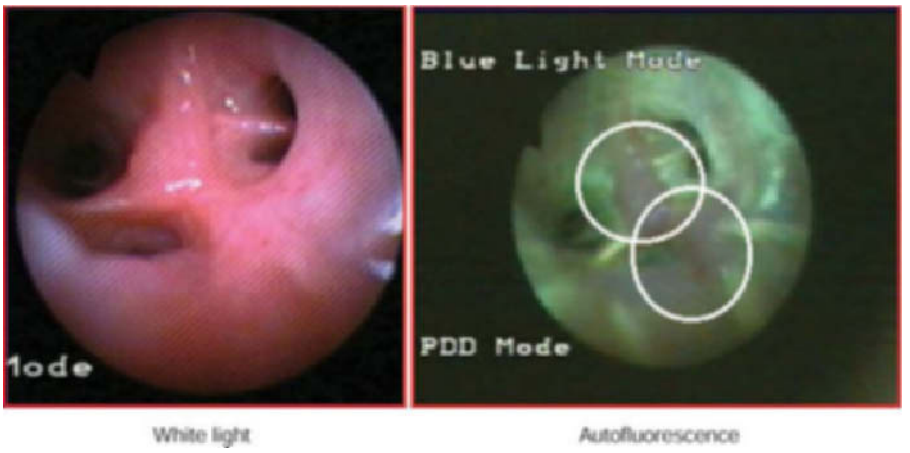

Figure 1.11 Carcinoma in situ: White light and autofluorescence images of carcinoma in situ in a bronchus. (Image produced with D-Light system, courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

xenon light source for cellular excitation. The xenon lamp uses an infrared blocking filter before light is transmitted via a liquid light guide. The image is then generated via a photodetection system using one black and white (B/W) CCD camera with a dual detection range: 500–590 nm and 600–700 nm. This imaging system produces independent green and red imaging, which is overlaid to produce the AF image. The DAFE system attempts to further improve upon AF technology by creating a simultaneous white light image via a color camera driver that has the red and green AF imaging superimposed upon the white light view. This concept allows simultaneous viewing of the airways with WLB and AF [40]. The DAFE system can be used with rigid bronchoscopes or the Wolf, Olympus or Pentex flexible bronchoscope systems (Figure 1.15a,b) [41].

The Onco-LIFE system (Xillix Technologies Corp., Richmond, British Columbia, Canada) is currently not available for sale with only preliminary studies having been performed at

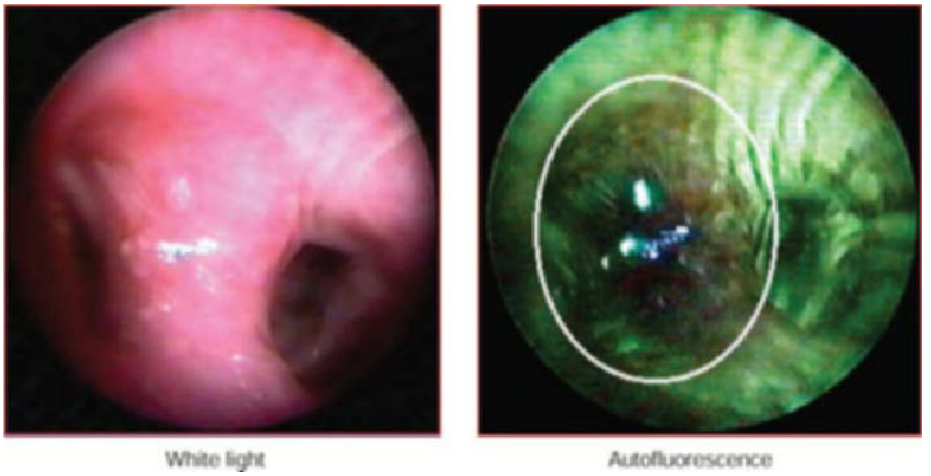

Figure 1.12 Microinvasive carcinoma: White light and autofluorescence visualization of a microinvasive cancer of the bronchus. (Image produced with D-Light system, courtesy of Karl Storz of America, Culver City, California, USA, with permission.)

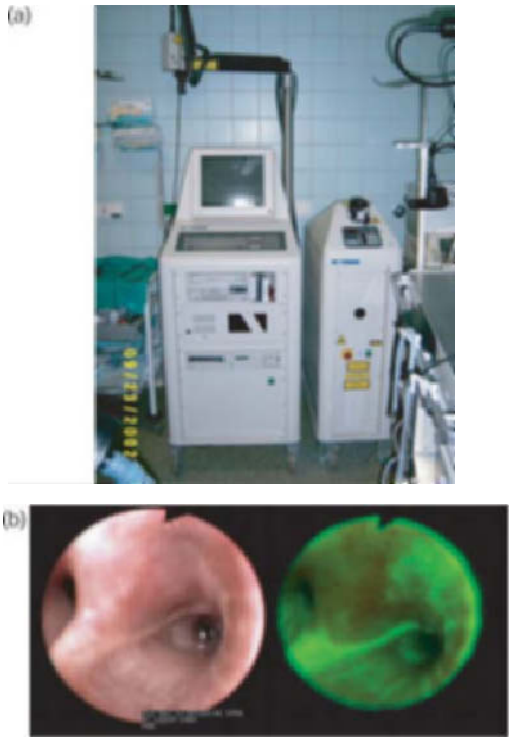

Figure 1.13 (a) The LIFE autofluorescence system. (b) White light and autofluorescence images produced with the LIFE system. (Xillix Technologies Corp. Richmond, British Columbia, Canada, reproduced with permission.)

the British Columbia Cancer Agency. The Onco-LIFE system uses a filtered mercury arc lamp for fluorophore stimulation. It then uses a low light sensor (ICCD) for fluorescence imaging. A color CCD sensor is incorporated into the system for improved white light visualization as well as for imaging of red in AF mode. These combined sensor inputs are put together to create the image visualized. Operators can use a footswitch or switch on the camera. The Onco-LIFE system is developed for use with any endoscope (both rigid and flexible) from Olympus, Pentax, Fujinon, Storz or Wolf (Figure 1.16) [42,43].

The System of Autofluorescence Endoscopy (SAFE) 1000 (Pentex Corporation, Asahi Optical, Tokyo, Japan) uses a xenon light source also, which is filtered to create a light with a wavelength of 420–480 nm. Reflectance filtration is used to improve visualization of AF. An image intensifier is incorporated into the system to improve distinction of the very low light autofluorescent changes. This system creates the distinctive green of typical background of normal mucosa with "cold spots" as areas of abnormality [44].

The D-Light system is currently the only FDA approved, commercially available system in the

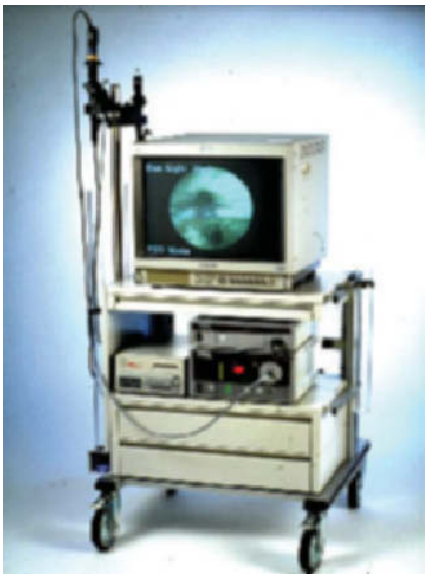

Figure 1.14 The D-Light autofluorescence system. (Karl Storz Endoscopy of America, Culver City, California, USA, reproduced with permission.)

United States. It is also sold and used in the rest of North America, Europe, Africa, South America, Asia and Australia [45]. The LIFE system is no longer available for fresh purchase, but continues to be used worldwide at those institutions that have this equipment. The DAFE system is commercially available in Europe, Asia and Canada; the company is considering further clinical trials [41]. OncoLIFE is currently not commercially available. Xillix Technologies Corporation states that the first published data will likely be the study carried out as part of the FDA regulatory approval process [42]. No communications were received from Pentex Corporation regarding the availability or plans of clinical trials for the SAFE 1000 system despite multiple attempts at contacting them.

Does it work?

One of the earlier clinical studies by Lam *et al.* [46] looked at 94 subjects, 53 with known or suspected

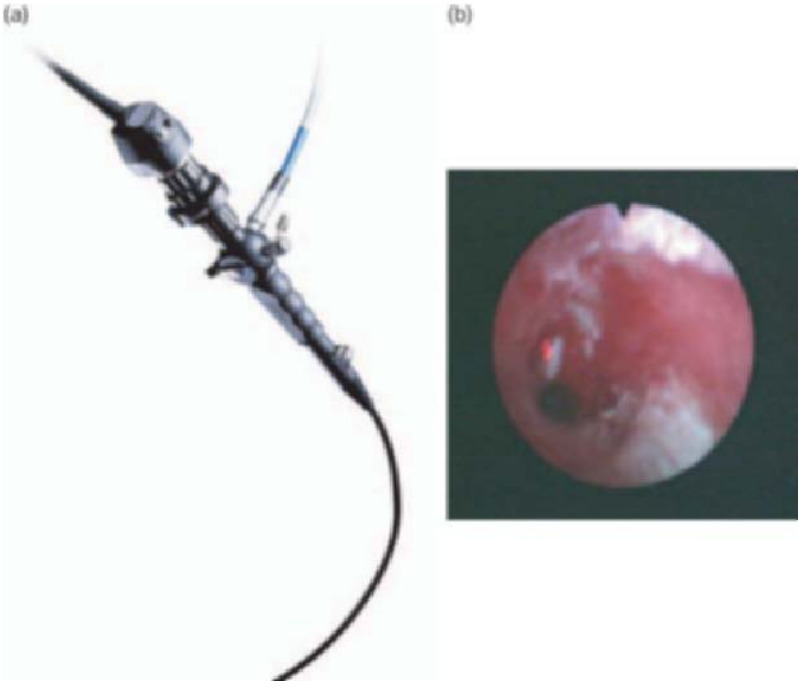

Figure 1.15 (a) The DAFE autofluorescence system. (Richard Wolf Endoscopy Gmbh, Knittlingen, Germany reproduced with permission.) (b) Image produced with DAFE system. Note red area, identifying area of cancerous or precancerous lesion superimposed on a white light view (Richard Wolf Endoscopy Gmbh, Knittlingen, Germany reproduced with permission.)

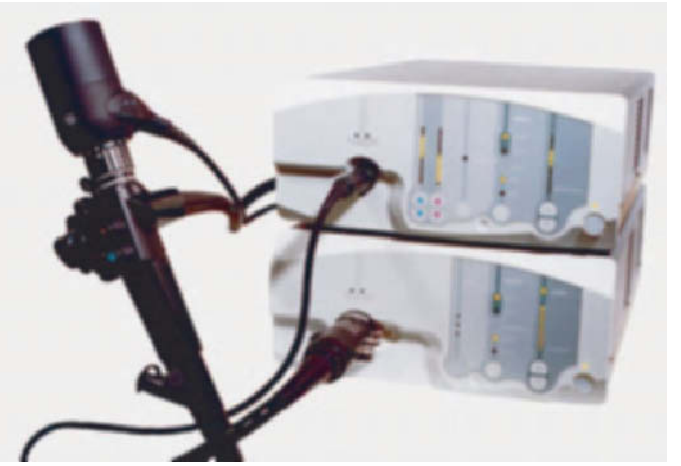

Figure 1.16 The Onco-LIFE autofluorescence system. (Xillix Technologies Corp. Richmond, B.C., Canada, reproduced with permission.)

lung cancer and 41 volunteers (17 smokers, 16 ex-smokers, 8 nonsmokers). All patients had WLB and autofluorescence bronchoscopy with a LIFE system immediately following the white light examination. All areas with changes consistent with early lung cancer were biopsied when identified by white light or AF techniques. WLB and AF bronchoscopy identified normal tissue and was also biopsied as a control. A total of 328 biopsy specimens were obtained during the 94 performed procedures. Sixty-four invasive cancers, 29 CIS, 62 areas of dysplasia and 173 normal biopsies were reviewed. The authors reported that for the detection of dysplasia and CIS, they had sensitivities with white light versus AF bronchoscopies of 48.4 versus 72.5% and specificities of 94 versus 72.5% for white light and AF bronchoscopies, respectively [46].

The pattern of improved sensitivity of AF bronchoscopy for the detection of early cancer and precancerous lesions is repeated throughout the literature. I compounded the information available in 11 clinical studies [24,46–54]. Included in these studies were 1084 patients who underwent 1289 bronchoscopies with 3487 biopsies. Matching data as well as was possible, a combined analysis of sensitivity and specificity was performed. The sensitivity of WLB versus AF was found to be 52.4 to 84%, respectively. Specificities for WLB and AF bronchoscopy were 87 and 78%, respectively. The only limitation in these studies that should be pointed out is that the sensitivity referenced in some cases is a relative sensitivity. The most recent review of the use of the LIFE system by Lam *et al.* reports a twofold improvement in the detection of precancerous lesions with AF versus WLB [55]. Currently, there is no gold standard available to identify all possible endobronchial lesions and therefore the actual sensitivity of AF cannot be determined.

Several clinical studies have also been performed using the D-Light system (Karl Storz Endoscopy, Tuttlingen, Germany) in Europe with encouraging statistical results for the identification of precancerous and early cancerous lesions [56–58]. A clinical study was recently completed in the United States with the Storz D-Light system using a very similar research protocol as those performed with the original LIFE studies. The six clinical sites involved reported a white light sensitivity of 10.6% versus the AF sensitivity of 61.2% for abnormal histology. The WLB versus AF specificities was 94.6 versus 75.3%, similar to the specificity relationship seen in previous LIFE studies [59].

Published clinical studies using the DAFE system are currently limited. The study by Goujon *et al.* reports on 20 patients who had WLB and AF performed during the same session, with comparison of identification of precancerous and cancerous lesions. They report a positive predictive value of 75% for AF versus 38% for WLB [40]. These findings with the DAFE system echo those of investigators using various AF systems. Other studies have been performed using the DAFE system for AF evaluation and follow-up of patients, but data

is limited [60–63]. Richard Wolf Endoscopy is, at the time of writing this chapter, in the process of making a decision about a larger clinical trial for their system [41].

The Pentex SAFE 1000 system has been compared to the LIFE system in two clinical studies [64,65]. No sensitivities or specificities are reported, but the authors of both studies suggest similar results were found when comparing the LIFE system to the SAFE 1000 system. Both studies also report a shorter time period involved in the examination with the SAFE 1000 system compared to examination with the LIFE system. The SAFE 1000 system appears to provide results, similar to those of the LIFE and D-Light systems that are being used clinically.

There are currently no clinical studies to compare the Onco-LIFE system to other AF systems or to WLB.

Overall, in these and other studies, AF has improved the diagnostic ability to detect early endobronchial cancer and precancerous lesions. Individual studies can be scrutinized for variances from each other and subtle discrepancies in technique from one another, but this would take us from one of the most important take home points: the technique of AF appears to improve the diagnosis of early cancers and synchronous cancers in patients with more advanced disease. I would emphasize that despite the repetitive comparison of WLB to AF throughout the literature, the most important issue to remember is that it is the combination of white light and AF bronchoscopy data that will be used for the evaluation and treatment of patients clinically. Therefore AF should be thought of as an additive tool to WLB rather than a replacement as is suggested in many studies.

Specificity is repeatedly better with WLB than with AF in all studies. The question that should now be asked is why AF sees this "normal" tissue as abnormal? Wistuba *et al.* have suggested that up to half of these false positive biopsies have some molecular genetic aberrations associated with malignancies despite their normal histology [55]. This concept seems to be supported by the fact that molecular aberrations associated with malignancy have been found in histologically normal mucosal biopsies of smokers in the past [12]. Conceptually, this is an exciting area of consideration. With improved knowledge of molecular clonal abnormalities being developed, it is postulated that the normal histologic findings may be a mask to true pathology [66,67]. Until a better understanding of the implication of genetic changes on the development of and/or natural history of premalignant to cancerous lesions is developed, this additional information remains a question rather than an answer and an area potentially ripe for research.

Clinical application of AF

Autofluorescence improves the way airways are examined, in conjunction with standard WLB airway examinations. Venmans *et al.* looked at their patient population, particularly those at risk for lung cancer who underwent both white light and AF bronchoscopy. They reviewed their data from 114 patients undergoing 224 bronchoscopies. On a per-patient basis the authors concluded that the addition of AF bronchoscopy to standard white light examination alone provided clinically relevant information in 13% of the bronchoscopies performed and/or in 16% of their patients. They defined clinically relevant findings as those biopsy specimens demonstrating moderate dysplasia, severe dysplasia or CIS [54].

Autofluorescence bronchoscopy in conjunction with WLB has been reported by other authors to change the management course in some patients. M.Th.M. van Rens and colleagues evaluated 72 patients with recently diagnosed non-small cell lung cancer or with highly suspicious lesions roentgenographically with WLB and AF. Up to six new high-grade endobronchial lesions were identified in 10 of the patients evaluated. Due to the findings in 3 of these 10 patients, definitive treatment was changed. The combination of WLB and AF techniques may add significantly to patient management by identifying synchronous lesions that would have otherwise gone undetected and therefore unmanaged [68].

Preoperative evaluation of the airways using AF has also been used to modify therapeutic interventions. Forty-three patients who had probable resectable roentgenographically visible lung cancer

had AF performed with 177 biopsies taken. Fifty-six metaplasias, nine dysplasias and four CIS were identified. These findings led to modification of the planned surgery in three patients, two of who received localized therapeutic treatment as the primary therapeutic modality. This study reports 9.3% prevalence of synchronous early lung cancers, metaplasias and dysplasias in the patient population studied [64].

Another study looked at a group of patients ($n = 23$) that had radiographically occult lung cancer and that was being assessed for intraluminal bronchoscopic treatment with curative intent. High-resolution computed tomography (HRCT) and AF bronchoscopy was performed prior to therapy. Of the 23 patients, 19 (83%) had no visible tumor or enlarged lymph nodes on HRCT. With AF bronchoscopy, 32% (6 of 19) of patients evaluated were found to have tumors of total area less than or equal to 1 cm^2 with clear-cut margins. These patients received the planned intraluminal therapy they were being assessed for. AF identified more extensive local tumor infiltration than was originally found with WLB alone in the remaining 13 patients. Of these patients 6 underwent surgical interventions; 7, with tumors that were inoperable, received external beam radiation and intraluminal therapy. Of the patients presenting for intraluminal therapy alone, 70% were identified as having more advanced disease requiring a more aggressive therapeutic program than was pre-AF expected [5].

As was previously mentioned, the progression of endobronchial pathology is recognized with, e.g. the conversion of severe dysplasias to a more advanced invasive cancer 19–46% of the time [15,16,69–71]. Bota *et al.* [20] investigated the natural history of precancerous lesions using AF. One hundred and four high-risk subjects had a baseline and follow-up AF bronchoscopy performed for evaluation of their airways. If, at the time of the initial AF bronchoscopy, the highest-grade lesion identified was a mild dysplasia or a lower grade lesion, follow-up AF bronchoscopy was performed in 1 year. If the highest-grade lesion identified was moderate dysplasia, follow up bronchoscopy was performed in 6 months, and a 3-month follow-up AF bronchoscopy was scheduled when severe dysplasia or CIS were found. Patient follow-up for the study was 24 months. The investigators found that 6 of the originally evaluated 36 normal epitheliums developed dysplastic lesions at the 1-year follow-up bronchoscopy. Metaplastic lesions were also followed at 1 year and 47 of the 152 initial metaplastic lesions evolved into dysplastic lesions, with 2 progressing to CIS and 1 to an invasive cancer. Of the original 169 low-grade dysplastic lesions 6 progressed to persistent severe dysplasia. Lesions that were initially found to be severely dysplastic progressed or persisted in 10 of 27 patients, with 28 of 32 CIS doing the same. The authors concluded by recommending a 2-year follow-up examination for patients with low-grade epithelial lesions. They also recommended that patients with high-grade, severe dysplastic lesions should be reevaluated in 3 months. If there is progression or persistence of the lesion, treatment should be instituted. Finally they suggest that CIS be treated immediately.

If we find early disease

> Early diagnosis and localization of lung cancer is an essential precondition for curative therapy.
>
> Vogelstein *et al.*,
> "The Multistep Nature of Cancer"

As techniques in interventional pulmonology continue to advance, the idea of intraluminal bronchoscopic treatment with curative intent is not as far fetched as it may have been in the past. In one small study, six patients were identified by AF to have endobronchial disease. These six patients then went on to have endobronchial ultrasound performed to evaluate each lesion as to the depth of tumor invasion. Of the six patients studied, two were found to have tumor only within the mucosa and submucosa, but not outside of the cartilage, and were treated with photodynamic therapy. Three of the patients with more advanced disease went on to surgical resection, with the final patient undergoing combined chemo and radiation therapy [72]. Although this approach may seem far from the norm now, as we look toward the future, this has the potential to become a more routine practice.

Various tools currently used in interventional pulmonology including neodymium, YAG

laser (0.7–3.0 mm tissue penetration), photodynamic therapy (1–2 mm depth of penetration) and cryotherapy (5–8 mm diameter of tissue destruction) can be considered for endobronchial therapy of more superficial precancerous/cancerous lesions [25,73,74]. Electrocautery, argon plasma coagulation and brachytherapy are other modalities that are also immediately available for endobronchial management. Furthermore, as our understanding of dysplastic evolution continues, advancements such as in chemoprevention may offer additional approaches to the management of early primary or synchronous lesions in patients at high risk and/or with lung cancer [69,75,76].

As advancements in optics and other endobronchial diagnostic technologies develop (i.e. microconfocal scanning microscopy endoscopic optical coherence tomography, endoscopic magnetic resonance tomography and doppler sonography) identification of earlier lesions may become vastly more important in the evaluation and management of our patients' early lesions that are found with AF. Concurrently, as our ability to look at the specimens we are collecting improves (histologic and molecular methods), it may further increase our ability to identify those biopsy samples not only with cancer, but also with a high degree of cancer potential. Park *et al.* [66] have demonstrated that molecular abnormalities in histologically normal bronchial specimens can be quite extensive. Of the samples reviewed by the authors, 68% had at least one abnormality among the chromosomal regions analyzed. The natural history of these genomic changes, as they are understood, will help with our planning and treatment.

Park *et al.*'s study also reported heterogeneity in the molecular changes seen, while endobronchial specimens identified and biopsied with the use of LIFE, which were histologically normal, demonstrated a high percentage of molecular abnormalities that were more homogeneous for the allele specific losses being investigated [66,67]. This type of data suggest that AF positive lesions that are sampled and are now being identified as histologically normal may in fact have precancerous molecular changes that we have not yet been able to clinically consider; yet, they are changing the cellular AF potential early.

Patient selection

Screening for lung cancer is still an area of great uncertainty. Attempts of screening with high-resolution CT, chest radiographs and sputum cytology continue to be looked at to find "the" ideal test. Bronchoscopy may give a tremendous amount of information of diseases of the central airways, but as a screening tool it is too invasive, expensive and would therefore be impractical. AF bronchoscopy should instead be considered an adjunct technique used in those situations where a fiberoptic bronchoscopy needs to be performed for more established indications. Patients who are undergoing bronchoscopy for the diagnosis and/or staging of a radiographically evident lesion should have AF bronchoscopy added to their airway evaluation. Those patients who are to have surgical resection should, be considered for AF evaluation of their airways preoperatively to potentially diminish the recurrence of cancer at the site of the surgical stump. Patients found to have abnormal sputum cytology should also have AF bronchoscopy as part of their evaluation in that the lesions leading to the abnormality may be small and not readily evident. High-risk patients who present with hemoptysis and require airway examination should also have AF bronchoscopy used in their evaluation to improve upon our diagnostic accuracy as to the source of the bleeding. The presence of precancerous lesions as well as synchronous and metachronous cancers is becoming better understood. AF is a tool to identify these lesions in patients, improving upon our opportunity for early diagnosis of lung cancer and possibly bettering our ability to treat this disease.

Conclusion

Autofluorescence is a technique currently available for clinical practice. The technology has been demonstrated to provide improved sensitivity in study after study for the detection of pre-neoplastic and early cancerous lesions. Much of the skepticism associated with the use of AF up to now has been in the interpretation of the data acquired, for instance, what do you do with a dysplastic lesion? As our understanding of how both the natural history and molecular changes influence the progression

of metaplasia to dysplasia to CIS continues to grow, the clinical importance of AF will certainly become more evident.

The technique of AF requires developing skills in looking and interpreting the color variations on the screen. A learning curve for the detection of early cancers is as common with a technique such as AF as in many procedures. In one study, the authors demonstrated improved sensitivities with AF in patients 49 through 95 (sensitivity 86%) versus the original 48 patients (sensitivity 67%) [52]. Once the skill and understanding of using AF bronchoscopy is acquired, it adds little time to a standard examination and the information gained can influence the overall management and very possibly long-term outcomes on our patients.

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2

CHAPTER 2

New technologies for the endobronchial assessment of the pulmonary tract

Mark E. Brezinski, MD, PHD

Introduction

In this chapter, we will be primarily examining optical technologies for endoscopically assessing pathology. Most of these technologies are emerging technologies and some will likely play an important role in the future of clinical medicine. The chapter is not designed to review all the pilot studies where these technologies have been applied to the pulmonary tract. Instead, it focuses on theory, strengths and limitations of these new technologies to allow the reader to better interpret data generated with these diagnostic tools in past and future studies.

For the purpose of this chapter, optics will be described as the study of the propagation of electromagnetic radiation (EM), of which light is a type of this radiation. An EM wave encompasses the spectrum from gamma rays to radio waves. The spectrum of EM waves by wavelength and frequency are shown in Figure 2.1. Gamma rays represent the high energy, short wavelength end of the spectrum while radio waves are low energy and have a long wavelength. EM is generated as atoms or molecules transition from a higher energy state to a lower energy state. As examples, gamma rays are generally generated from energy state nuclear transitions within the nucleus, while visible light is generated from energy state transitions of outer electrons. This chapter will focus attention on those technologies that use EM between the ultraviolet and infrared regions. We will use the definition of light as that radiation existing between the visible and near infrared regions.

Very briefly, EM waves represent the propagation of energy in space and time through electrical and magnetic fields. From the laws of physics, EM arises because a changing electric field results in a magnetic field and a changing magnetic field results in an electric field. Therefore, this ability of one changing field to generate another results in a self-propagating wave. With EM, the electric field is perpendicular to the magnetic field and both are perpendicular to the direction of light propagation. This concept is illustrated in Figure 2.2a. Since the EM wave is self-propagating, in a vacuum, an electromagnetic wave can travel indefinitely.

EM, at all wavelengths, has several important properties. First, the speed is the same for all EM, 3×10^8 m/s, what is often termed the speed of light. Second, the wavelength of EM is related to the frequency through the formula:

$$\lambda \nu = c$$

Here, λ is the wavelength, ν is the frequency, and c is the speed of the wave. Third, EM has the property that it can be polarized, meaning that the electric field (and therefore the magnetic field) has a specific orientation in space. For example, EM can be polarized in the x direction, meaning that the electric field oscillates only in the x plane. The topic of polarization is reviewed in greater detail in cited references, but it should be noted that light can be

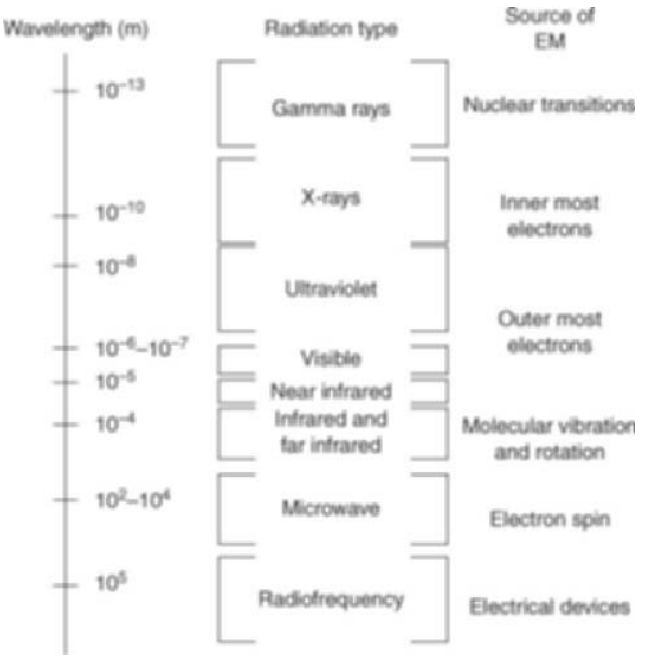

Figure 2.1 The spectrum of EM waves by wavelength and frequency.

linearly, circularly or elliptically polarized as well as unpolarized [1,2]. Figure 2.2 shows two linear polarized states, which are perpendicular or orthogonal. Fourth, EM also has the property that it can behave either like a particle or wave depending on the circumstance. This very complex topic is well beyond the scope of this text, and involves the quantum nature of light [3]. But briefly, when EM behaves like a particle, it is referred to as a photon (which has discrete values or are quantized) and the energy of the photon can be described by the formula $E = h\nu$, where E is the energy, h is Planck's constant, and ν is the frequency. In general, when large numbers of photons are involved, light behaves as a wave. When small numbers of photons are involved, light behaves like a particle. Finally, the velocity of EM generally changes when going from one medium to another. The parameter used to define the change of velocity for a given medium is referred to as the refractive index [1]. There are many reasons why the refractive index is important; one is that when EM goes from a medium of one refractive index to another, the direction of propagation of the light is changed.

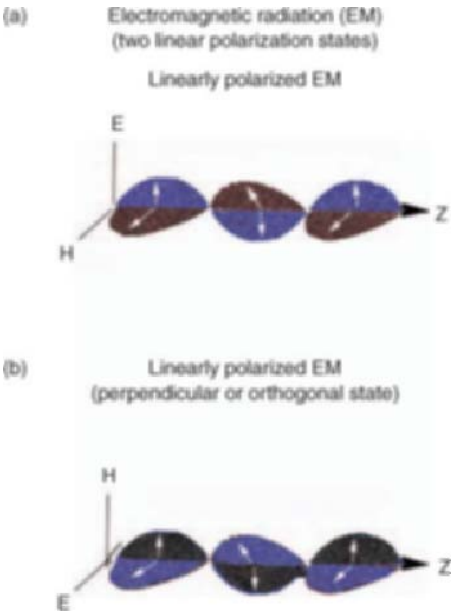

Figure 2.2 Two linear polarized states.

When EM propagates through materials that are not homogeneous, such as tissue, its forward intensity is reduced (attenuation) through a combination of absorption and scattering. These phenomena of scattering and absorption are used as the basis for most of the technologies that will

be discussed in this chapter. Since atoms and molecules have specific energy levels (whether electronic, vibrational or rotational transitions), they are capable of absorbing photons of discrete energy values, as dictated by the laws of quantum mechanics. Some of the techniques that will be discussed depend on the phenomena of absorption, which will be discussed in greater detail later in the chapter.

Scattering is when EM interacts with an atom, molecule or particle and the properties of the scattered EM, particularly the direction, are changed. Scattering of EM is dependent on the refractive index mismatch between the scatter and the medium, the size of the scatter and the shape of the scatter [4]. Scattering is used by techniques such as optical coherence tomography (OCT) and Raman to assess the properties of tissue. Scattering might be elastic or inelastic. Elastic scattering occurs when photon maintains its original energy while inelastic scattering results in a change in energy of the scattered photon. The change in energy results in changes in frequency and wavelength.

Technologies

The technologies that will be discussed can be divided into either spectroscopic and/or structural imaging techniques. In general, spectroscopic techniques depend on measurements of the absorbing properties of tissue, which to a large degree assess biochemical parameters, while structural imaging depends predominately on the scattering properties of tissue. This distinction is somewhat of an oversimplification since there is some overlap between the technologies, but it is sufficient for the purposes of this chapter.

Structural imaging

The optical technologies that will be discussed, which characterize the properties of tissue through assessing tissue morphology or structure, include OCT and confocal microscopy. In addition, a brief mention of a nonoptical technology, high frequency ultrasound, will be made since it is generally considered a competitive technology.

Optical coherence tomography

Optical coherence tomography is a recently developed micron scale imaging technology that has shown considerable promise as a diagnostic medical technology [5,6]. OCT is analogous to ultrasound, measuring the intensity of backreflected infrared light rather than sound. It has several advantages as an imaging technology for biomedical imaging. First, the resolution of OCT is between 4 and 20 μm in most tissue, up to 25$\times$ higher than anything available in clinical medicine [7]. Second, OCT is fiber based, allowing catheters to be both inexpensive and to be designed to have very small cross-sectional diameters, with the current smallest OCT catheters being in the range of 0.014 in [8]. Third, OCT is compact and portable, approximately the size of an ultrasound machine. Fourth, OCT is near real time, allowing data to be obtained at close to video rate [9]. Fifth, OCT imaging does not require direct contact with tissue or a transducing medium, and can therefore be performed through air. Finally, OCT is optically based, allowing it to be combined with a range of spectroscopic techniques, such as polarization spectroscopy [10]. Polarization spectroscopy allows the assessment of organized collagen and elastin, which gives important information on tissue characterization.

As stated, some analogies exist between OCT and ultrasound. OCT measures the intensity of backreflected infrared light and uses it to produce a two-dimensional backreflection profile or image, but at a much higher resolution than ultrasound. The time for the light to be reflected back or echo delay time is used to measure distances in a manner analogous to ultrasound. However, unlike ultrasound, the echo delay time cannot be measured electronically due to the high speed associated with the propagation of light. Therefore, the technique of low coherence interferometry is used to measure the echo delay time. This technique allows micron scale ranging.

With low coherence interferometry, a beam splitter divides light from the source. Figure 2.3 shows a schematic of the OCT system. In the simplest configuration, half the light is directed at the sample and half at a moving mirror. Light reflects off the mirror and from within the sample. If light in both arms has traveled the same optical distance, when recombined at the detector, interference will occur.

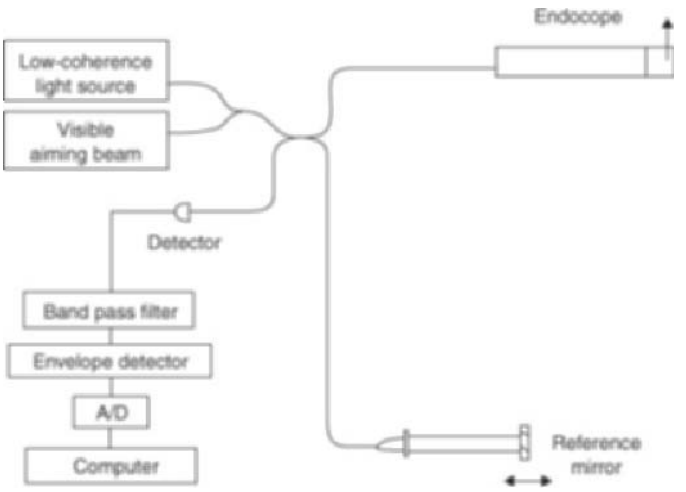

Figure 2.3 A schematic of the OCT system.

OCT measures the intensity of interference and uses it to assess backreflection intensity. By changing the optical pathlength in the reference arm, which in the simplest case occurs by moving the position of the mirror, backreflection intensity can be measured from different distances within the tissue.

OCT power sources use ultrashort light pulses or low coherent light, which is the basis for the high resolution achieved. For the purposes of analogy, low coherent light can be viewed as a series of short pulses. The shorter the pulse, the more closely the optical path lengths in both arms must match for interference to occur. If the "pulse" was extremely broad in duration, the backreflected light from within the tissue would come from a relatively large area within the tissue and interference would occur from scattering within this large region. By using a low coherence source or ultrashort pulse laser, backreflection information is obtained only from very small regions within the tissue, allowing for high resolution ranging.

The ability of OCT to perform high-resolution assessment of tissue microstructure has been demonstrated in a wide range of organ systems *in vivo*, including the respiratory tract. The images produced are equivalent to a low to moderate mechanical level biopsy obtained during diagnostic procedures, at micron scale resolutions and roughly over the distance of a biopsy, 2–3 mm. Images produced are obtained at very high data acquisition rates, which means that many "optical biopsies" can be performed without any tissue removal. Clinical trials are underway [11].

Confocal microscopy

Conventional microscopy typically illuminates a wide area with a condenser lens. This configuration allows light from outside the focus to enter the aperture, reducing the resolution. The smallest object resolvable by conventional light microscopy can be calculated using the Abbe equation [12]:

$$Z = 0.6\lambda/\mathrm{NA}$$

where Z is the resolution, λ is the wavelength and NA is the numerical aperture of the objective lens. The NA is defined as $\mathrm{n}\sin\theta$ which represents the ability of the optics to collect light and is a common optics arameter used to define the properties of the system [1]. In this equation, θ is the half-angle of the light collected by the objective. For angles greater than θ light can no longer be accepted by the system (i.e. lens). Since we are generally dealing with tissue that have a refractive index greater than air, the NA must be corrected for the refractive index of the medium (n) being viewed.

The limit of the lateral resolution for conventional microscopy, which is wavelength dependent, is of the order of 0.2 μm. The length of the focus in the axial direction is referred to as the depth of field. For a conventional microscope, the depth of field is on the order of a few microns. Therefore,

there exists a significant difference in lateral and axial resolution. This difference in the lateral and axial resolution degrades the overall image being viewed. In addition, if the specimens are thick, scattered out-of-focus light from different planes lead to even further optical deterioration.

Due to the limitations of conventional microscopy, confocal microscopy has recently become popular. Although Marvin Minsky first patented the confocal microscope design in 1957, its general acceptance took decades and commercial systems were not available until the late 1980s [13]. Confocal microscopy eliminates much of the limitations of conventional microscopy by having a smaller field of depth and rejecting much of the out of focus information. It does this by requiring illumination and detection to occur at the same point [14]. To achieve this, the illumination optics and detection optics must be near perfectly aligned. This is usually done by using the same lens for illumination and detection. This coalignment is shown in Figure 2.4. The objective lens simultaneously focuses on a pinhole between the lens and the detector. Light returning from the focus passes through the pinhole and onto a detector. Out of plane light returning from above or below the focal point is focused behind or in front of the pinhole, reducing or eliminating its contribution and/or interference, there by improving resolution. A lateral scan generator is also present to allow information to be obtained from an x–y plane rather than a single point.

The axial resolution with confocal microscopy is determined by the size of the pinhole relative to the magnification and NA. The smaller the pinhole at a given lens parameter, the higher the resolution of image generated. When the pinhole size approaches the diffraction limited spot size of the focused light from the lens, the resolution can no longer be improved with reductions in the pinhole size. If the system is diffraction limited, the maximal axial resolution is given by [12]:

$$Z = 2n\lambda/(\mathrm{NA})^2$$

Maximal lateral resolutions with confocal microscopy can be in the range of 0.5 μm with depth resolutions of 0.5 μm. Unfortunately, confocal

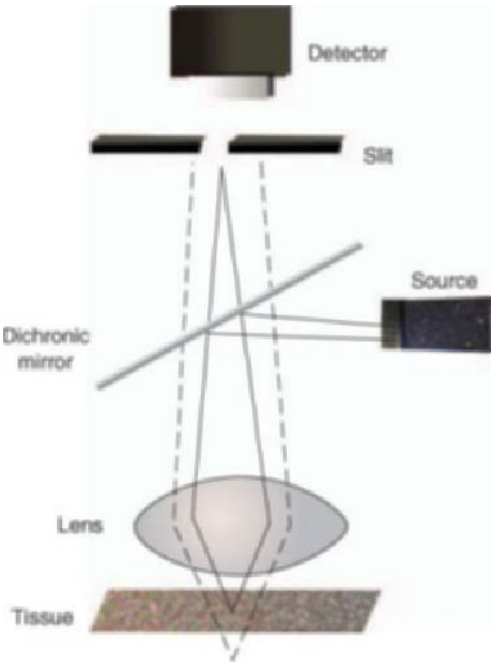

Figure 2.4 A schematic of confocal microscopy showing the coalignment of the illumination and detection optics.

microscopy does have several disadvantages for diagnostic imaging. First, in highly scattering tissue, which represents most biological tissue, its penetration is only in the range of 100 μm. Second, imaging is typically performed in the x–y plane, which makes it more difficult to interpret than the usual x–z data obtained with technologies such as ultrasound and OCT. Finally, confocal typically requires direct contact with the tissue, making it impractical for routine use in many clinical scenarios. However, confocal remains a powerful tool in experimental biology and some endoscopic applications have shown promise, particularly the bladder [15].

A recent modification of endoscopic confocal microscopy is spectrally encoded confocal microscopy [16]. This approach uses a quasi-monochromatic light source and a transmission diffraction grating to detect the reflectivity at multiple points along a transverse line within the sample. The method does not require fast scanning within the probe since this function is taken over by the grating. Therefore, the equipment may ultimately be miniaturized and incorporated into a catheter or endoscope. Therefore, it represents

another "optical biopsy" technique, although only over a few 100 microns.

High frequency ultrasound

Although high frequency ultrasound is not an optical technology, it deserves discussion because it is sometimes considered a competitive technology to most of the other modalities discussed in this chapter. Sound generally propagates through a medium via mechanical compress and expansion, although some transverse component can occur under the right circumstances. Ultrasound (or echocardiography when imaging the heart) is a technology commonly performed in medicine, which uses sound waves for diagnostic purposes. When the term ultrasound is used, it generally refers to sound waves with a frequency greater than that which can be detected by the ear (>20 kHz). Ultrasound is used in a manner analogous to that described for OCT. Acoustical waves are generated at the sample or tissue. The time for the sound to be reflected back, or echo delay time, is used to measure distances. The echo delay time is measured electronically.

Standard clinical devices use vibrating disks or plates (the transducer) to generate ultrasound waves. These disks serve both as the source of ultrasound waves and as the detector. Transducers are typically made of crystals such as lead zirconate titanate (PZT) or polyvinylidine difluoride (PDVF) [17]. If voltage is placed across the transducer (crystal), it will expand and if it is reversed, the crystal contracts. The voltage across the crystal controls the relative size and rate of change of the transducer. If an alternating current is placed across the transducer, it will change in a sinusoidal manner. The changing shape of the transducer results in a sound wave that compresses or expands the adjacent medium. The deformation propagates through the tissue. As stated, the crystal serves both as a sound generator or detector so that, if the detector receives backreflected acoustical waves, voltage is generated by the transducer that can be detected electronically.

For distance measurements, pulsed ultrasound is used for reasons analogous to that described for OCT. Also, similar to OCT, the shorter the pulse duration (or larger the bandwidth), the greater the resolution of the image produced [18]. The principles as to why backreflection of sound occurs in tissue are very similar to that of light, except that the mismatch of acoustical impedance (density/velocity of sound) rather than the refractive index is the source of scattering. Scattering theory with respect to size and shape of the object is also similar to that of light, generally covered under what is known as Mie's theory [19]. Sound is a wave; it is not surprising that it has many physical properties similar to light. For instance, sound exhibits diffraction and interference when coherent just like light. An important difference between light and sound is that the attenuation of light is minimal (as in OCT imaging) but much more significant than sound waves. Due to these limitations, ultrasound imaging, for all practical purposes, cannot be performed in air and requires a transducing medium.

The ultrasound transducer can either be single or an array [18]. For single detectors, focusing, for the purpose of imaging, is performed either by having a curved piezoelectric array or through the addition of an acoustic lens. If the outer ring of the array is energized first, then the rest of the ring is activated sequentially inward; the different waves coming from the various transducers interfere in such a way to form a focus. Since the different rings can be controlled electronically, the focus is adjustable with system electronics. The lateral resolution of ultrasound is therefore dependent on the properties of a lens-like system, similar to an optical lens as was previously described. Similar to light, the smaller the focus, the shorter the distance over which the focus is maintained or in other words, the spot size falls off rapidly.

Ultrasounds axial resolution is increased with increasing frequency and decreasing bandwidth. However, there is a tradeoff between frequency and penetration. The higher the frequency of ultrasound wave produced, the less the penetration. The penetration is approximated by the formula:

$$\text{Penetration (cm)} = 40/\text{frequency (MHz)}$$

Currently, the ultrasound system used clinically with the highest resolution is the 40 MHz intravascular imaging catheter, which has an axial resolution of approximately 80–90 μm [20]. The

penetration is of the order of a few millimeters, similar to that of OCT.

While the resolution of high frequency ultrasound is high, although far less than that of OCT, it has several significant disadvantages relative to pulmonary endoscopy. First, since the transducer is present within the endoscope, the endoscope size must be relatively large and expensive. Current endoscopes have a cross-sectional diameter in the range of 1 mm, which have been used in applications such as evaluating the gastrointestinal tract. Second, ultrasound cannot be performed effectively through air. Therefore, a transducing medium is required which is difficult to implement in the respiratory tract. This is currently attained by the use of a fluid filled balloon that must occlude the entire airway.

This is how ultrasound is currently being used. Third, the crystal used must be the emitter or detector at any given time. Therefore, only a finite time period exists for the transition between emitting and detecting, leading to artifacts.

Light scattering spectroscopy

Light scattering spectroscopy is similar to the technology known as elastic scattering [21]. It is a relatively low "tech" technology, but has yet to be proven as useful as a diagnostic modality. Light scattering spectroscopy is based on the scattering spectrum of single scattered light. Scattering is due to the interactions with microstructures, generally nuclei and mitochondria. Since malignant cells exhibit a variety of morphologic abnormalities including nuclear enlargement, nuclear crowding and hyperchromasia, the theory is that it will be able to distinguish malignant from normal regions. Unfortunately, to date, light scattering spectroscopy remains largely untested *in vivo*. Due to this limitation, the author has elected not to discuss the technology in further detail.

Spectroscopic techniques

Spectroscopic techniques are based upon alterations of the wavelengths of the emitted light from tissue rather than directional changes in the incident light directed toward tissue. While there is some clinical overlap between spectroscopic and structural imaging techniques, spectroscopic techniques assess the biochemical properties of the tissue while structural techniques assess the physical orientation of microstructure within tissue.

Fluorescence

Fluorescence can be divided into point measurements and imaging. The initial discussion will focus on point measurements, then we will move on to the most recent techniques of multiwavelength fluorescence imaging.

Fluorescence has become a very popular technique for studying cellular processes [22,23]. In large part, this is due to the wide range of high quality fluorescence probes and labeling protocols. However, its broad based clinical application to *in vivo* imaging of humans has been limited.

Fluorescence is an area of investigation that has been present for decades. Fluorescence is the absorption of photons followed by emission of a photon at a longer wavelength. The theory behind fluorescence can best be illustrated in the Jablonski diagram shown in Figure 2.5. In this diagram, S_0 is the resting state while S_1 is the first excited state. These energy levels are different electronic states that are dictated by the rules of quantum mechanics. It should be understood that, for a given atom or molecule, the electrons (and rotational states) are only allowed to have discrete values. The electrons change in response to various stimuli that excite them to a raised energy state. Why these specific energy levels are allowed, yet others are not, can be explained through basic quantum mechanics, but are well beyond the scope of this work. Reference texts on the topic are listed for those interested [3]. In the Jablonski diagram, the S_1 and S_0 states are also subdivided into sublevels that, in this case, represent different vibrational levels of the molecule at the given electron excitation state. There is also a T_1 level, which corresponds to an electron transition to an energy level with a different electron spin state from S_0 and S_1, which are in the same spin state. Once again, the reason for the different energy levels of the electron spin transition fall under the rules of quantum mechanics, playing an important role in how absorbed energy is dissipated in cells.

When light normally interacts with a molecule, it is scattered in the order of 10^{-15} s, which for

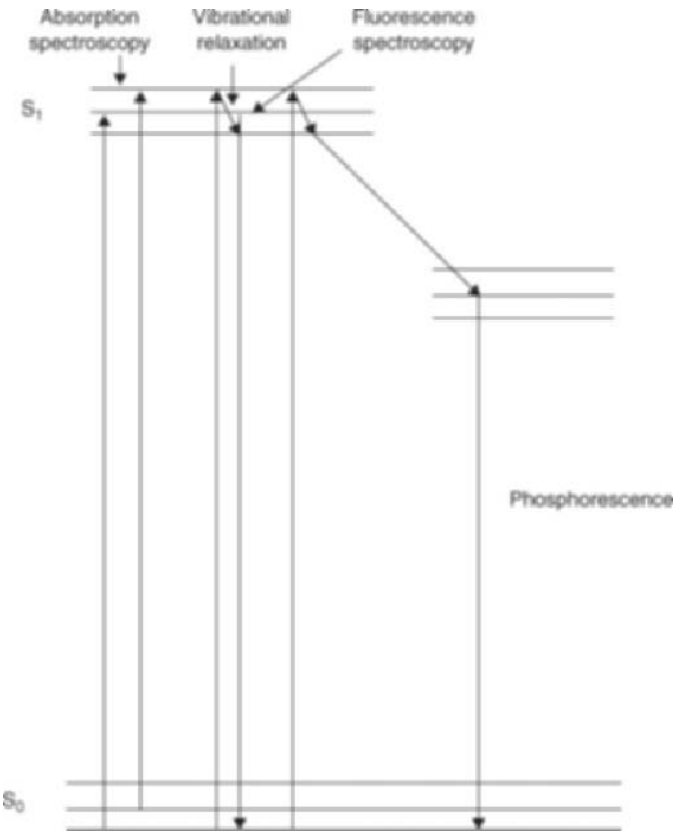

Figure 2.5 The Jablonski diagram where S_0 is the resting state while S_1 is the first excited state.

practical purposes can be considered essentially instantaneous. This corresponds to the normal scattering process of light. However, the light can undergo transient absorption, partially losing its energy into the cell the light is emitted, often at different wavelengths. This is the process of fluorescence.

To begin with a simple example of the process of fluorescence, a quantum of light ($h\nu$) is absorbed. This results in the transition of the molecule from the S_0 state to the S_1 state. Since the S_1 state has various energy states that are closely spaced, the molecule will undergo internal conversion, where the electron drops to the lowest S_1 state, its lowest excited vibrational state. This event occurs in a picosecond interval. Therefore, since the electron is in the lowest S_1 state, all energy will be released from this lowest S_1 state.

There are three pathways by which the electron drops out of the S_1 state. These are emission (fluorescence), nonradiative relaxation and transition to the T_1 state (triplet state).

With fluorescence emission, a photon is released but, since internal conversion has led to a loss of energy due to drop to the lowest S_1 level, the emitted energy is at a lower energy level than the incident light and therefore a longer wavelength. Fluorescence occurs when a photon is absorbed, then emission takes place in the order of 10^{-8}–10^{-10} s. Among the properties of fluorescence that are of diagnostic value are the Stroke's shift, shape of the emission spectrum, fluorescence lifetime and to some degree the nonradiative losses.

As stated, the emitted photon will have a lower energy than the incident photon. This reduction in energy and frequency is known as the Stroke's shift. When separated from the incident light and other fluorophores (fluorescence producing molecules), it gives information about the fluorophore being evaluated as well as the local

environment. Environmental factors that influence fluorescence include ion concentration, pH and the presence of molecular interactions.

The emission spectrum, which is the distribution of emission as a function of wavelength, also has diagnostic value. The fluorescence emission does not occur at a single wavelength but at the transition from S_1 to S_0 occurs to the various ground state vibrational levels of S_0. As seen in Figure 2.5, the S_0 contains various sublevels due to different vibrational and rotational energy levels.

Besides the Stroke's shift and emission spectrum, the fluorescence lifetime can also be used for diagnostic information. The *average* time for the molecule to go back to the ground state is known as the fluorescence lifetime. The fluorescence lifetime (τ) is given by the formula:

$$\tau = 1/(\alpha + \kappa)$$

Here αg is the rate of transition from S_1 to S_0 and κ is the transition back to S_0 through non-fluorescence mechanisms. The fluorescence emission profile has a shape that is exponential in nature. While individual molecules have their own lifetimes, τ is also dependent on the local environment, which alters the lifetime. The fluorescence lifetime has several advantages. First, it can help distinguish molecules with similar Stroke's shift but different lifetimes. Second, the lifetime measurements are a property of the molecule, so they are predominately independent of probe concentration relative to fluorescence intensity.

Fluorescence emission, as stated, is not the only mechanism by which the molecule can drop to the S_0 state. This can occur through either nonradiative transitions or by crossover to T_1 states. Examples of nonradiative transitions include resonance energy transfer and collision quenching. Resonance energy transfer occurs when the molecule in the excited state transfers its energy to another nearby molecule, before emission can occur, through electromagnetic interactions. Collision quenching occurs when the excited molecule collides with another molecule capable of removing the absorbed energy before emission can occur. Molecular oxygen is a common example of a quenching molecule. Both these mechanisms compete with fluorescence emission.

The third mechanism that competes with fluorescence is the crossover to the triplet state (T_1) rather than directly to S_0. A single electron has one of two spin states and T_1 represents a different spin state from S_0 and S_1, which poses a significant energy barrier for transition to S_0. While in the T_1 state, which is at a lower energy level than S_1, the molecule can release energy through emission (known as phosphorescence) or through the nonradiative mechanisms previously described. In general, phosphorescence occurs at a much slower rate and intensity than even fluorescence.

Another important mechanism for decreased fluorescence emission is photobleaching. When a fluorescent molecule has undergone repeated excitation, the molecule becomes irreversibly damaged and they can no longer emit fluorescent light. This phenomenon is referred to as photobleaching and is highly dependent on the intensity of the light exposure, the probe type and the environment. Photobleaching can have a detrimental effect on interpreting fluorescence data.

Fluorescence can be endogenous or can be from autofluorescence [24]. Autofluorescence occurs when compounds intrinsic to the tissue demonstrate fluorescence. Examples of molecules that exhibit autofluorescence include the pyridines/flavins (e.g. NAD, FAD, etc.), aromatic amino acids (e.g. tryptophan, tyrosine and phenylalanine), structural proteins (such as collagen and elastin) and eosinophilic granules. Examples of exogenous fluorophores include 5-aminolevulinic acid (ALA), bis-carboxyethyl carboxyfluorescein and porphyrins. Disadvantages to the presence of exogenous fluorophores are the side effect of photosensitivity with stimulation that can last for weeks, requiring avoidance of sunlight.

In addition to point measuring fluorescence techniques, which have been discussed to this point, there are also fluorescence based imaging techniques. These techniques acquire data at a single point and may be impractical for use in screening the bronchial tree. In order to attempt to overcome this issue is the technique of ratio fluorescence imaging (RFI) [25]. RFI consists of simultaneously measuring fluorescence in the green and red regions of the wavelength spectrum. The ratio

between red and green is used to distinguish normal tissue from premalignant or malignant tissue. The data is present in pseudocolor and presented in real time. The normal mucosa when stimulated appears as green while dysplastic cells and carcinoma appear predominately red. One original commercial system, known as LIFE (light-induced fluorescence endoscopy), was developed by Xillix Technology (BC, Canada) to evaluate the airways for autofluorescent variables [26].

While fluorescence can give information about tissue characteristics, the technology has been around for a considerable period of time and still has not found clear clinical indications. One reason for this is that large-scale clinical trials generally show unacceptably high sensitivities or specificities, depending on where the baseline is set. There are likely a variety of reasons for these results; one may be due to the fact that the biochemical baseline of tissue varies significantly from individual to individual. This includes not only differences in fluorophores, but also differences in local environments, nonradiative relaxation and photobleaching. In addition, tissue architecture, absorption (particularly hemoglobin), scattering, the metabolic state of the tissue and the biochemical environment can lead to serious variations in measurements. All these suggest that fluorescence as a diagnostic technique can be limited by variation from patient to patient, narrowing its usefulness as a diagnostic tool.

Two-photon laser scanning microscopy

Two-photon laser scanning microscopy (TPLSM) is a technique which should be discussed because of its future potential and because it is a competitive technology to confocal microscopy [27,28]. With confocal microscopy, the incident light typically uses a wavelength at or near the UV region, which may be damaging to tissue. In addition, there is a relative lack of appropriate lens as for use in the UV region. With two-photon fluorescence, the fluorophore absorbs two lower energy photons simultaneously, which typically but not always have the same wavelength. The two photons combine to excite the molecule to the S_1 level. The photons generally are in the red or near infrared regions, which have lower energy and are therefore safer for the tissue.

High laser intensities are required to induce this two-photon absorption. Saturation and photobleaching will occur if a continuous wave source is used. Instead, short pulse lasers, of the order of femtoseconds (10^{-15}), are used which have high peak powers but the same average power. The laser is therefore focused to a very small focal point (the diffraction limit) so that the laser intensity drops off rapidly both in the lateral and axial directions. Excitation volumes can be in the range of 0.1 μm^3. In general, imaging produces depths of the order of 300–600 μm.

TPLSM requires no pinhole-like confocal microscopy. Furthermore, the galvanometer mirror in a confocal microscope leads to some loss of returning light (half), but TPLSM does not contain this descanning mechanism, improving fluorescence collection. Ignoring tissue properties, the sensitivity to emitted photons with TPLSM is therefore dependent on the numeric aperture, throughput of the microscope, and the efficiency of the detectors.

The major disadvantage of TPLSM is the cost and size of the femtosecond lasers. Additionally, there is currently incomplete data on two-photon fluorophores and due to this clinical usefulness has not yet been evaluated.

Near infrared absorption spectroscopy

Absorption spectroscopy, which has been studied for well over half a century, is based on the fact that molecules absorb energy at specific wavelengths. In theory, the backreflection profile over a range of wavelengths will incorporate the absorption profile (lose backreflected light) of the tissue; where specific wavelengths have been absorbed there will be no signal. In the near infrared region, where most diagnostic absorption imaging is currently being performed, absorption is occurring predominately by molecular bond transitions of vibrational and rotational modes [1]. For the purposes of illustration, atoms in a molecule can be viewed as being connected to each through springs. When EM is applied to the bond, in this case infrared radiation, it leads to oscillation of the bond. This oscillation leads to a change in the displacement of the maximal and minimal distance between the two atoms in the bond or "spring." Usually, the vibrating bond acts like an oscillating dipole and reradiates the infrared light at the same wavelength

that it was stimulated, but in different directions. This is the basis of scattering. However, these "springs" or bonds have certain specific frequencies, known as resonance frequencies, under which the EM photons are absorbed rather than reradiated. Each of these are specific frequencies to the type of bond and/or molecule. Once absorbed, de-excitation occurs when energy is lost through dissipation into the molecule (heat) or by emission of a less energenic photon. One of the biggest problems associated with absorption spectroscopy is that water makes up the largest constituent of tissue and its absorption spectrum overshadows that of virtually all other molecules. In addition, bond energies vary with environmental conditions. Some recent techniques using algorithms and statistical analysis have shown some promise for assessing tissue characteristics [29]. However, the acquisition rates remain relatively slow and the technology remains largely untested on a large scale.

Raman scattering

While the Raman effect involves a change in the wavelength of light, it is an instantaneous process and actually a form of scattering rather than traditional absorption. Therefore, it can occur at a wide range of wavelengths. It is based on changes induced in the rotational and vibrational states of the molecular bonds induced by infrared light. Most scattering between light and molecules is elastic; the energy of the photon striking the molecule is the same as that of the emitted light. About one in every million collisions is inelastic and involves a quantitative exchange of energy between the scattered and incident photon. With the Raman effect, monochromatic light is scattered by a molecule. A frequency shift then occurs above and below the incident light in a small fraction of the light scattered, which is known as the anti-Stroke's and Stroke's shift [30]. This shift is independent of the frequency of the incident light but the intensity varies with the fourth power of the frequency of the incident radiation. The Raman effect occurs when a beam of intense radiation passes through a sample containing a molecule that can undergo a change in molecular polarizability as they vibrate. Raman is somewhat distinct from infrared absorption since changes in the polarizability are of more importance than that of the dipole moment. Polarizability is distinct from the classic dipole radiation; the electron cloud around the molecule elongates and contracts under the EM in a manner distinct from the resting state or normal modes.

Symmetrical molecules have greater Raman effects than asymmetrical molecules, an effect which is opposite from traditional absorption. The intensity of fluorescence produced may therefore be orders of magnitude higher than the Raman effect, completely obscuring the Raman spectrum. This is why Raman spectroscopy is performed in the near infrared. This frequency has been chosen to lie below most electron transitions and above the fundamental vibrational frequencies. The biggest disadvantage of Raman spectroscopy, in addition to its low sensitivity, is that the number of high-energy photons required may result in tissue damage and concurrently reduced penetration. It should also be noted that a relatively long time is required to obtain data, making its clinical viability questionable. It takes roughly 5 s to take a single Raman spectrum measurement with reasonably low signal to noise ratio.

Conclusion

Optical technologies represent promising new tools for the endoscopic assessment of the bronchial tree. These technologies provide information currently not available through standard imaging technologies and many provide new advances for endobronchial diagnostic techniques.

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3 CHAPTER 3

Endobronchial ultrasound

Felix J.F. Herth, MD, DSC, FCCP *& Heinrich D. Becker,* MD, FCCP

Many pathologies of the airways involve the bronchial wall and the parabronchial structures. Unfortunately, radiological imaging has been proven to be unreliable in defining pathological involvement of these structures [1,2]. The view of the endoscopist however is limited to the lumen and the internal surface of the airways (Figure 3.1a,b). Indirect signs, such as bulging or mucosal changes, can only be used to assess disease within the airway wall and outside the airways. Especially in malignancies this can be of decisive importance for the fate of the patient and planning of therapeutic interventions. Therefore, expanding the endoscopist's view beyond the airways is essential [3].

Endoluminal ultrasound has been established as a routine diagnostic procedure in other fields of medicine due to its diagnostic advantages over traditional radiologic evaluations [4]. This is especially true of gastrointestinal endoscopy, where endoluminal ultrasound has become firmly established in staging of esophageal carcinoma, carcinoma of the cardia and rectum, in the diagnosis of primary tumors and lymph node metastasis, as well as involvement of the neighboring structures [4–7]. For these indications, endoluminal ultrasound has had decisive influence upon diagnostic and therapeutic procedures. In the investigation of mediastinal and parabronchial structures external transthoracic ultrasound has been applied with some success. Lesions of the anterior mediastinum and the subcarinal region have been well visualized, but the lower paratracheal structures and peri-hilar anatomy are usually out of reach [8,9].

Prior to the availability of endobronchial ultrasound (EBUS), endoesophageal ultrasound (EUS) was initially used to assess the lymph nodes in the chest. Yet, even with EUS, the pretracheal region and the hilar structures remained inaccessible to ultrasound assessment due to limited contact and interposition of the airways. It was due to these limitations that from 1989 onward we have been investigating the application of ultrasound technology endobronchially [10,11].

The development of endobronchial ultrasound

The imaging in ultrasound is different from the images created through other x-ray technologies. Ultrasound imaging is generated due to the difference in resistance of various tissues to ultrasound waves (impedance). Impedance is partially dependant on tissue water content, but other tissue factors influence imaging. The different impedance of various soft tissues has made ultrasound an indispensable diagnostic tool in medicine. Due to the size of the airway lumen instruments that are used for gastrointestinal applications could not be readily applied inside of the airways, their diameter being to large. The preliminary experience of using miniaturized endovascular sonographic probes did not yield useful clinical results and were subsequently aborted after a while [12]. We therefore developed flexible catheters and for application inside the central airways a balloon tip was added to the Olympus probe (Figure 3.2), which allows the probe circular contact within the airways for the ultrasound (Figure 3.3), providing a complete 360° image of the parabronchial and paratracheal structures. The saline filled balloon

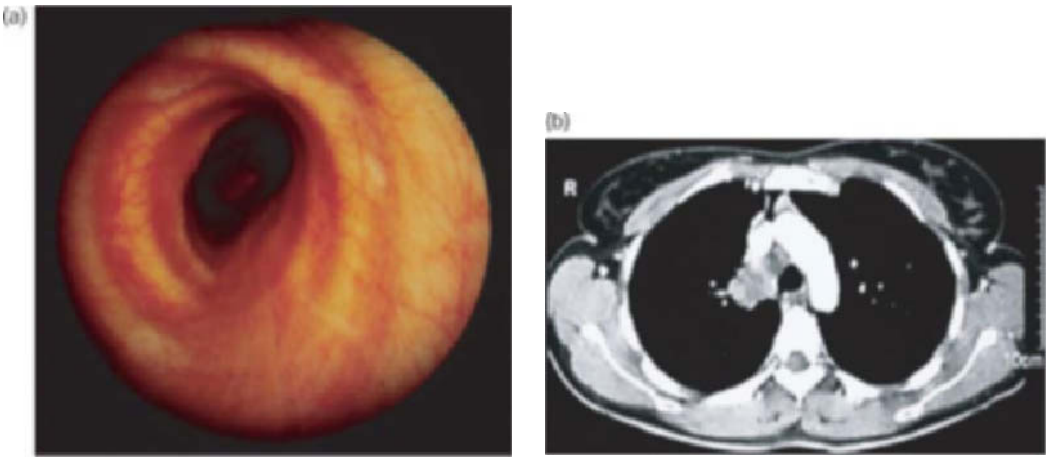

Figure 3.1 Compression of the trachea by tumor (a). The corresponding CT scan shows the tumor adjacent to the trachea and cannot be separated from the tracheal wall due to extinction of the mediastinal fat (b).

Figure 3.2 The miniature probe (UM-3R) and balloon catheter (MH-246R).

Figure 3.3 Tip of a fiberscope with probe and filled balloon.

provides improved delivery of the ultrasound waves to the structures of the mediastinum (ultrasound waves are not transmitted through air). The ultrasound waves are produced by a 20-MHz generator and delivered via the probe. Thus, under favorable conditions structures at a distance of up to 4 cm can be visualized using EBUS (Figure 3.4). The probes have been in the market since 1999 and can be applied with regular flexible endoscopes that have a biopsy channel of at least 2.8 mm (for more technical details see References 10 and 11) (Figure 3.5). Prototypes of dedicated bronchoscopes with an integrated curvilinear electronic transducer at the tip have not been widely applied so far [13]. Even complete obstruction

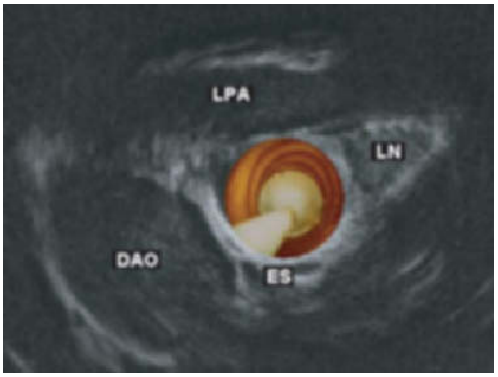

Figure 3.4 The balloon is filled with water and gains complete circular contact. On the composed image the structures surrounding the left main bronchus can be seen: the descending aorta (DAO), left pulmonary artery (LPA), esophagus (ES) and an enlarged lymph node (LN).

Figure 3.5 Ultrasound system by Olympus Company, consisting of processor (EU-M 30), driving unit (MH-240), keyboard and monitor. The miniature probe (UM-R) and balloon catheter (MH-246R) are introduced via the working channel of the fiberscope.

of the trachea with an ultrasound balloon can be tolerated under local anesthesia for up to 2.5 min after sufficient pre-oxygenation and proper sedation, which is sufficient for acquisition of diagnostic images [14].

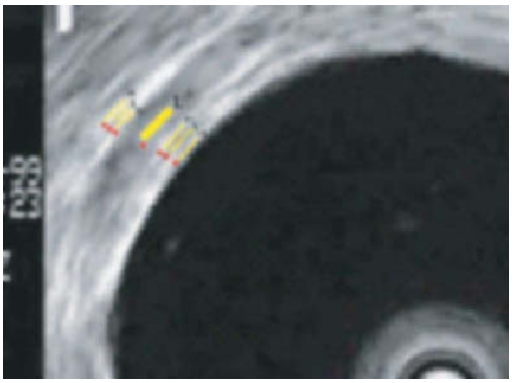

Figure 3.6 Sonoanatomy of the tracheobronchial wall *in vitro*.

Sonographic anatomy

The wall of the central airways is a seven-layered structure, which can be demonstrated only with high magnification ultrasound. The layers represent: the mucosa and submucosa, the three layers of the cartilage and the adjacent external structures of loose and dense connective tissue, respectively (Figure 3.6) [15]. Under low power magnification (20 MHz) and in the periphery only a three-layered structure is visible ultasonographically.

Orientation by ultrasound within the mediastinum is difficult [16]. In addition to the complex mediastinal anatomy; motion artifacts by cardiac and vascular pulsations and respiratory efforts interfere with interpretation of ultrasound data. In addition to this, the unusual planes of the ultrasonic images created due to the oblique angles of the airways as compared to the mediastinal structures also makes EBUS orientation difficult. Therefore, for orientation the analysis of characteristic ultrasound imaging of anatomical structures is more reliable than observation of the position of the ultrasound probe inside the airway to determine orientation within the thorax (Figures 3.7a,b and 3.8a,b) [11].

For instance, vessels can be identified by their pulsation. Yet even with the use of echo contrast media, discrimination of venous and arterial vessels can be difficult due to the great number of anatomic variations found. Despite this, arterial pulsations can be ultrasonographically distinguished by using a pulse oximeter with an audible pulse while performing the procedure. The visible vascular pulsation is then synchronized with the acoustic signal

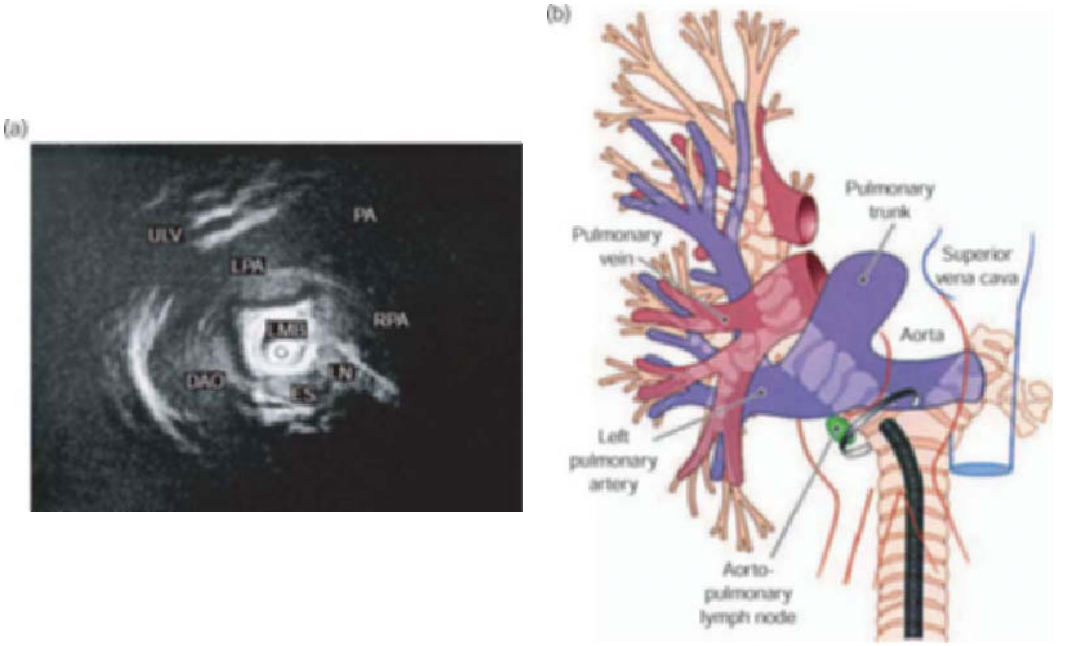

Figure 3.7 Sonoanatomy (a) and corresponding anatomical sketch (b) of the left main bronchus (LMB) which is surrounded by the esophagus (ES), the descending aorta (DAO) and the left (LPA) and right pulmonary arteries (RPA) that arise from the pulmonary main stem (PA). Ventralto the left pulmonary artery the left upper lobe vein (ULV) crosses. Adjacent to the esophagus a lymph node (LN) is seen.

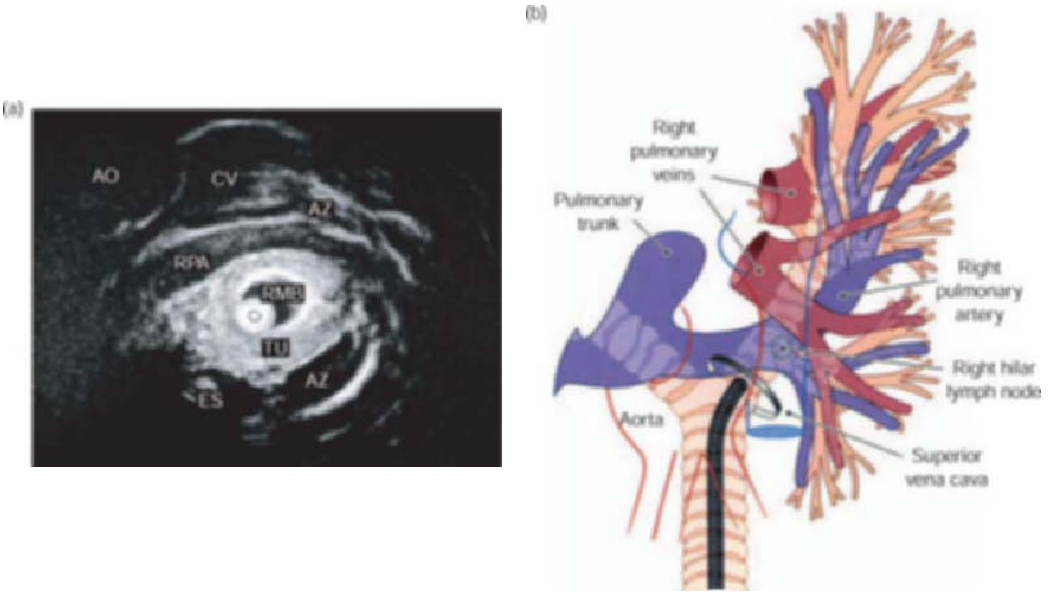

Figure 3.8 Sonoanatomy (a) and anatomical sketch (b) of the right main bronchus (RMB). Ventral to the right pulmonary artery (RPA) the vena cava can be recognized besides the root of the aorta (CV). Adjacent to the dorsal bronchial wall the esophagus (ES) is cut obliquely where it crosses behind the bifurcation to the left side. The azygos vein (AZ) runs alongside it in ventral direction, crossing the tracheobronchial angle and joining with the cava. The dorsal wall of the bronchus is thickened and its structure is destroyed by tumor infiltration (TU).

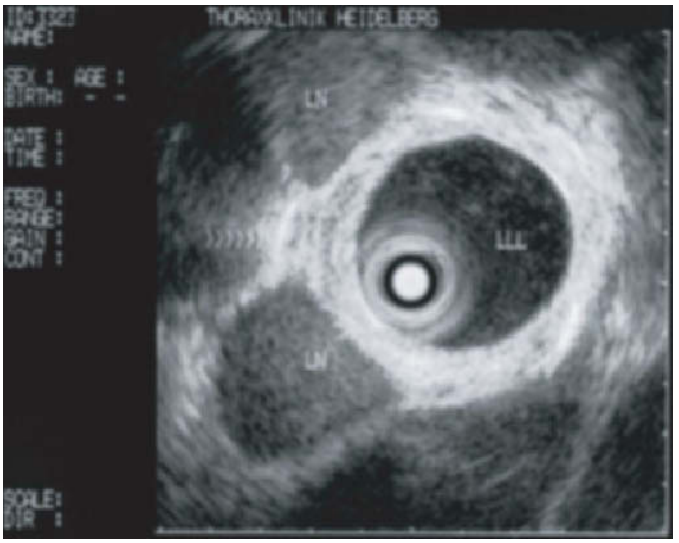

Figure 3.9 Sonography of a lymph node (LN) in the lower left lobe (LLL).

of the pulse oximeter to distinguish arterial vasculature. Venous pulsations are out of synch with the pulse oximeter. Lymph nodes and other solid structures can be differentiated down to a size of few millimeters from the blood vessels by their higher echodensity (Figure 3.9).

Indications and results of endobronchial ultrasound

Since the early 1990s we have been involved in developing the technology of EBUS. Clinical use of EBUS has grown with the commercial availability of the miniaturized probe since 1999. Endobronchial ultrasound is now being applied in specialized centers worldwide. The superiority of EBUS for some indications (see later) in comparison to conventional imaging has been demonstrated in prospective studies [17]. EBUS most readily visualizes endoluminal, intramural and parabronchial structures. With respect to this, indications for the use of EBUS include: the evaluation of early detected endobronchial and peripheral lesions, lung cancer staging, evaluation of inflammatory destruction of the airways, distinguishing mediastinal lesions as well as malformations of mediastinal structures in respect to tumor invasion versus impingement (Table 3.1).

Table 3.1 Indication for endobronchial ultrasound (1996–2001).

	%	(*n*)
1. Bronchial cancer		
• Intraluminal extension	12	(693)
• Invasion/limpression	21	(1214)
• Early cancer	14	(813)
• Vascular invasion	3	(165)
• Posttherapeutic controls	2	(119)
2. *N*-staging (incl. guided TBNA)	32	(1850)
3. Mediastinal mass evaluation	4	(230)
4. Pediatric bronchoscopy	5	(292)
5. Peripheral lesions	4	(231)
6. Postoperative controls	3	(175)
Total	100	(5782)

Cancer staging

Early cancer

For small radiological invisible tumors the practice on endobronchial therapy is becoming more common. The decision to use only local endoscopic therapeutic intervention is dependent on the intraluminal and intramural extent of a cancer within the different layers of the bronchial wall. In contrast to radiological imaging, endobronchial ultrasound can identify very small tumors only

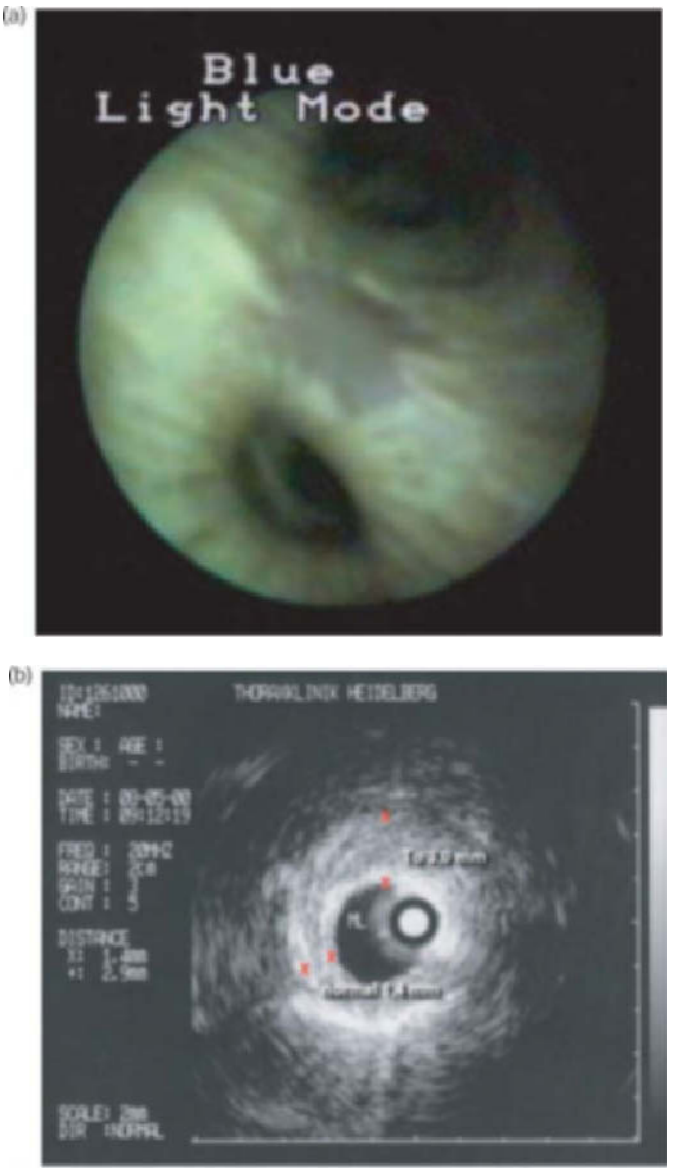

Figure 3.10 Autofluorescence image of a class 3 lesion (lingula) (a). EBUS image shows thickening of the wall (b) (Tu, tumor). Histological squamous cell lung cancer.

a few millimeters in size. Furthermore, we are now learning to analyze the image and differentiate malignant from benign lesions (Figure 3.10a,b). As Kurimoto *et al.* demonstrated EBUS is a very reliable tool in evaluating the extent of these small lesions [18]. We have demonstrated that by using EBUS on small autofluorescence (AF) positive lesions that were negative in white light bronchoscopy (WLB) we could improve specificity (predicting malignancy) from 50 to 90% [19]. The combination of EBUS with AF has been demonstrated to be efficient in prospective studies and has become the standard for curative endobronchial management of malignancies at some institutions [20].

Peripheral lesions

For histological diagnosis of peripheral intrapulmonary lesions by bronchoscopy an instrumental

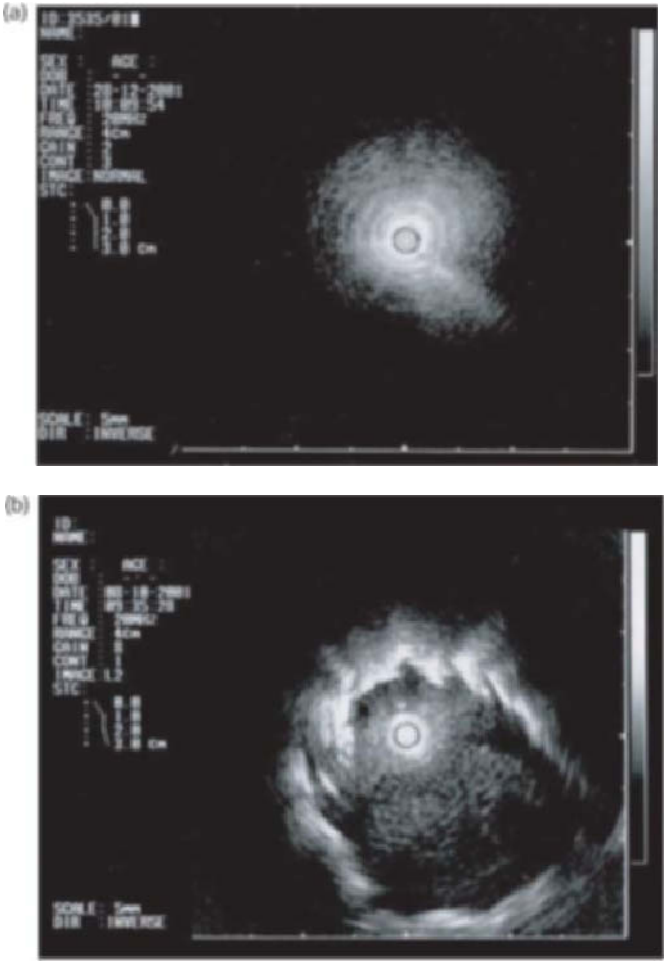

Figure 3.11 EBUS image of air-filled peripheral lung with the typical "snowstorm like" appearance (a). The image obtained when entering solid tissue in the periphery (b). A definite hypoechogenic signal can be appreciated.

approach under fluoroscopic or computed tomography (CT) guidance is currently the standard procedure. This demands expensive X-ray equipment in the bronchoscopy suite or coordination with the radiology department, and places patients and staff at risk of radiation exposure. In a recent prospective study we were able to demonstrate that these peripheral lesions could be approached by EBUS guidance with a similar success rate (75%) to biopsies performed with fluoroscopic guidance (Figure 3.11a,b) [21]. Recently, this data was reproduced by a group of Japanese bronchologists [22]. From preliminary data, we may also be able to not only localize these peripheral lesions, but predict the nature of the lesions, as malignant tissue seems to be different in its density spectrum from benign lesions [23]. These early studies strongly suggest that the use of EBUS for diagnosing peripheral lesions may become a standard approach to this problem in the future.

Advanced cancer

In preoperative staging EBUS allows detailed analysis of intraluminal, submucosal and intramural tumor spread which can be essential for the decision on resection margins. EBUS has proved especially useful in evaluating mediastinal tumor involvement. CT often cannot clearly differentiate between tumor approximation and tumor

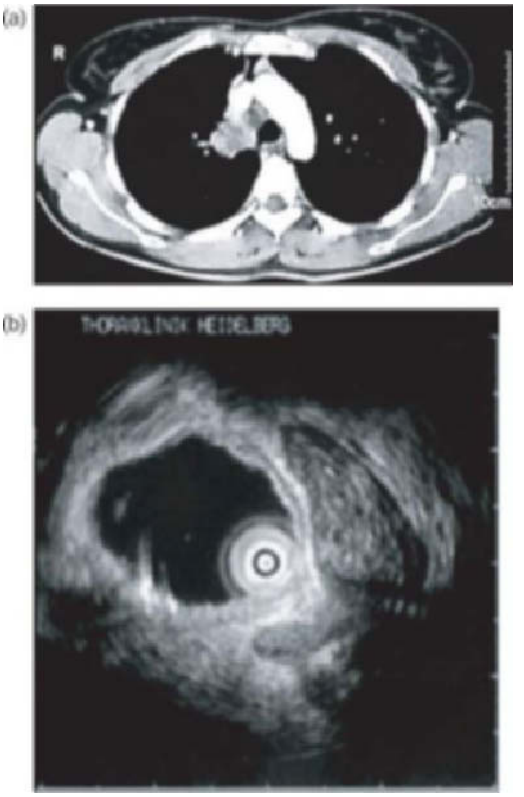

Figure 3.12 Example of a chest CT with central mass abutting the airway (a). This mass was classified as infiltrating the airway. (b) The corresponding EBUS exam demonstrating an intact outermost airway layer and as such no evidence of infiltration. The EBUS finding was confirmed at time of surgery.

invasion of the mediastinal structures. EBUS can be used to assess many of these structures like the great vessels: the aorta, vena cava, main pulmonary arteries, esophageal wall, which by conventional radiology frequently is impossible. In a prospective study we demonstrated that differentiation of external tumor invasion from impression of the tracheobronchial wall by EBUS is highly reliable (90%) compared to contrast to CT imaging (50%) (Figure 3.12a,b) [24]. Thus many patients considered to be non-resectable by the radiologist due to supposed T4 tumors could be operated in a curative approach after EBUS. For this purpose we successfully applied the miniaturized probes in the esophagus as well to exclude tumor invasion.

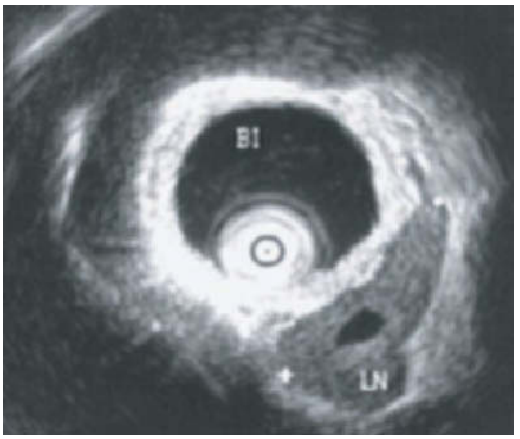

Figure 3.13 Lymph node (LN) with a central vessel (BI, bronchus intermedius).

Lymph node staging

Lymph nodes can be detected by EBUS down to a size of 2–3 mm under favorable conditions. The internal structure (sinuses and folliculi) as well as small lymph vessels can often be visualized (Figure 3.13). In contrast to previous publications [25] our experience with endosonographic localization of lymph nodes has led to sensitivities of 90% with transbronchial needle aspiration (TBNA) [26]. This is most significantly emphasized for those nodal positions in which reliable landmarks on the CT are missing (e.g. high and low paratracheal locations). It should be noted that there is a significant difference in EBUS *guided* TBNA as compared to EUS *controlled* biopsies performed by gastroenterologists. The esophagus is a straight elastic organ without any clear endoscopic landmarks for orientation. Without landmarks, it is essential to visualize the actual aspiration under sonographic control. In contrast, the tracheobronchial tree is full of landmarks for orientation such as cartilage rings, spurs and branches. Thus even very small lymph nodes can be safely localized by EBUS and sequentially the needle can be inserted successfully into the lymph node under endoscopic control after the miniature probe is removed from the biopsy channel (Figure 3.14).

EBUS in therapeutic interventions

Especially for decision in potentially curative endobronchial therapy of malignancies such as

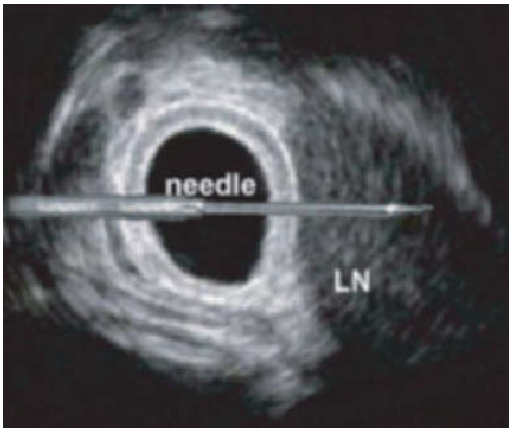

Figure 3.14 Animation of needle in a lymph node.

photodynamic therapy (PDT) or endoluminal high dose radiation (HDR) by brachytherapy evaluations as to the extent of the lesion in respect to the bronchial wall or to those structure in close vicinity of the area to be treated is essential. Here EBUS is superior to all other imaging procedures due to the detailed visualization of the tumor in respect to the layers of the bronchial wall (Figure 3.15a,b).

When endobronchial therapy of lung cancer is entertained, EBUS provides important data for clinical decision making [20]. EBUS can also be used for assessment of complete airway obstruction. The entirety of the tumor can be assessed, providing information to the endoscopists regarding the depth of penetration of the tumor in relationship to the different layers of the bronchial wall, how far the tumor is penetrating into the mediastinal structures and whether the airways beyond the stenosis are patent. Concurrently, patency of the adjacent pulmonary artery can be established, which is important to predict post-interventional perfusion of the involved lung in face of complete airway obstruction. This evaluation will potentially prevent an increase of dead space ventilation when non-perfused segments are reopened [26].

Endobronchial ultrasound is also useful for evaluation of benign central airway stenosis to assess the extent and in some instances the cause of the disease. Interventional planning is also assisted by understanding the relationship to vessels and other surrounding structures as well as helping to guide the appropriate therapeutic approach: mechanical dilatation, laser ablation, stent implantation or surgery [27].

Conclusion

In conclusion, with regard to the technique clinical application and the diagnostic results produced, EBUS is a routine procedure in our institution. Studies have been performed to help establish indications for the use of endobronchial ultrasound in diagnosing and managing intrathoracic disease as compared to conventional radiological methods and other diagnostic procedures.

The limitations of current imaging procedures of the parabronchial and mediastinal structures have led to the development and use of EBUS. By adapting the miniaturized 20-MHz probes to the special requirements inside the airways a clinically useful tool was developed. After establishing a normal sonographic anatomy of the bronchial structures and the mediastinum we investigated the feasibility of clinical applications of EBUS. Endobronchial ultrasound proved to be useful in high-resolution imaging of the multilayer structures of the bronchial wall and the adjacent mediastinal structures for a distance of up to 4 cm from the airway. In many instances EBUS was found to be superior for staging of lung cancer and other pathologies than traditional approaches.

Due to the fact that results of treatment of advanced bronchial carcinoma have been disappointing so far, detection and treatment of lung cancer at early stages continues to gain increasing interest. New technologies including automated sputum cytology analysis in persons at risk for lung cancer and localization of radiological and macroscopically occult carcinoma by fluorescence methods will be used more widely in the future. Previous to EBUS, lymph nodes could be easily localized for TBNA when they had reached a size greater than 1 cm, but tumor infiltration of the airways and surrounding structures could not be predicted. Using EBUS, other pathologies such as vascular malformations, mediastinal masses, pathologies of neighboring organs and pulmonary lesions can be correctly diagnosed using less invasive techniques. The benefits of EBUS may be particularly evident in on-the-spot decision

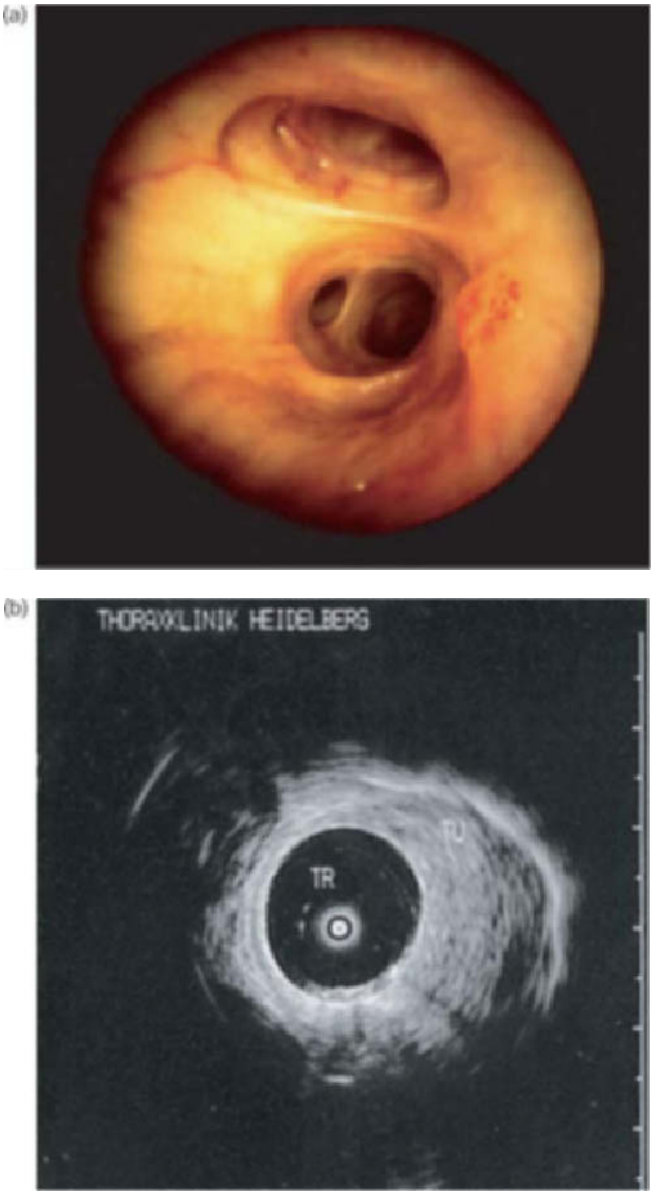

Figure 3.15 Endoscopic image of a small lesion in the airway initially thought to be a carcinoma in situ and referred for photodynamic therapy (PDT) (a). EBUS of the airway demonstrating significant tumor extension into the submucosa with violation of the exterior wall. PDT would most likely not reach the entire tumor and surgical resection is the better option (b).

making during diagnostic and interventional procedures as our understanding of this technology improves. Thus, we come to the conclusion that in the near future EBUS may play an important role in bronchology, both clinically and at a reasonable cost.

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, e.g. in control of bronchial anastomosis after surgical procedures. Further computerized analysis of tissue characteristics could be useful in the early diagnosis of malignancy. We therefore strongly believe that EBUS will be a routine procedure in the future and will play an important role in diagnostic and interventional bronchoscopy.

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4

CHAPTER 4

Advances in diagnostic bronchoscopy: virtual bronchoscopy and advanced airway imaging

Rex C. Yung, MD, FCCP *& Leo Patrick Lawler,* MB, BCH, BAO, FRCR

Thoracic imaging, whether by planar radiography or by axial and multiplanar tomography, is standard in the evaluation of most, if not all pulmonary conditions. This is because of the lack of specificity of many pulmonary symptoms such as dyspnea, cough and even hemoptysis, and of the similar lack of sufficient sensitivity and specificity of physical and laboratory findings for specific serious disease entities, ranging from acute pneumonia to carcinoma. From the perspective of even the most enthusiastic and experienced bronchoscopist, there is the acknowledgment that the visible airways represent only a small subset of the lungs' airways, even with advanced endoscopy camera systems, smaller caliber and highly maneuverable bronchoscopes and other guided instruments. An accurate understanding of the relationship of the steerable airways to an area of interest in the lung parenchyma (infiltrative or mass), and to surrounding vital intrathoracic structures (vascular, cardiac, esophageal, etc.) is paramount in maximizing the chance of success and in minimizing potential risks and complications from diagnostic and or interventional bronchoscopy procedures [1,2].

Paralleling the growth in diagnostic and interventional chest procedures are the expanding arrays of diagnostic thoracic imaging techniques. Some of these are refinements or new interpretations of existing imaging data, such as the manipulation of volumetric computed tomographic (CT) data to create three-dimensional (3D) rendering of intrathoracic structures. In addition software to link sequential multiplanar images creates the possibility of a virtual trip down the airways as in virtual bronchoscopy (VB). Other imaging techniques facilitate diagnostic or therapeutic procedure by providing realtime "live" imaging of thoracic structures, such as "fluoroscopic-CT" endobronchial ultrasound (EBUS). Some of these real-time imaging techniques such as optical coherence tomography (OCT), or *in vivo* Con-focal Laser-scanning microscopy (CLSM), have sufficiently high resolution to realize the potential promise of becoming an imaging *in vivo* biopsy technique. Metabolic imaging techniques, such as with 18-Fluoro-Deoxy-Glucose Positron Emission Tomography (18-FDG-PET) or octreotide scanning, provide additional pre-procedure guidance as to the location and sequence of how best to sample suspicious lesions to confirm and stage thoracic malignancies. The intensity of the metabolic uptake by tissue may also be of prognostic significance in predicting the rate of growth and likelihood of dissemination of cancer. The continued advances in thoracic imaging technology include the melding of different technologies such as the introduction of PET-CT combined scanners that permits much

more accurate anatomic localization of metabolic abnormalities.

This chapter will review the current CT techniques and the evolution of 2- and 3D post-processing tools, including VB of ever-greater fidelity to actual fiber-optic bronchoscopy examinations. Due to the rapid technological advances in CT imaging, the state of the art for airway imaging must largely reflect multidetector row helical CT (MDCT) and volume rendering (VR) 3D reconstruction [3–6]. A discussion of CT of the lung parenchyma and mediastinal structures is beyond the scope of this chapter but we will review some applications as they pertain to airway imaging. The basic principles of airway magnetic resonance imaging (MRI) will be addressed with an introduction to the developing concepts of imaging gas exchange. An overview of the current clinical applications will be given with suggestions for practical implementation of other advanced airway imaging most relevant to the diagnostic and interventional bronchoscopist. A glossary of some of the current terminology is provided.

Patient preparation for airway CT

Patients are imaged supine without any particular pre-scan preparation but for ascertaining whether he or she may have intravenous contrast dye allergy, the removal of overlying metallic artifacts and placement of the arms above the head. If the subject is intubated, ventilator settings may need to be adjusted to limit respiratory motion artifact, bearing in mind fast-MDCT scan times reduce the need for prolonged suspended respiration. Similarly, MDCT acquisition speeds limit the need for conscious sedation in infants and younger children. Routine coverage is from the thoracic inlet subglottic airway to below the diaphragm, but imaging of the nasopharynx to include the supraglottic air passages can be performed as well when requested. Noncontrast studies suffice for most airway imaging studies although intravenous iodinated contrast is preferred when there are concerns regarding adjacent masses or lymphadenopathy, or when systemic or pulmonary CT angiography is also required. When appropriate the esophagus is best delineated with the use of oral contrast paste. Most scans are performed during full inspiration only. To limit radiation exposure, inspiration and expiration imaging is performed only when there are specific clinical questions regarding tracheobronchomalacia, suspicion of regional air trapping and where such scanning may influence management.

Computed tomography techniques, physics and nomenclature

With the ready availability of helical or spiral CT, and the introduction of multidetector row helical CTs (MDCT), a routine chest study of 25–30 cm may now be imaged in a single breath hold of 10–15 s, providing 1 mm sliced widths and near-isotropic or isotropic (similar in all dimensions) voxels approximating $0.8 \times 0.8 \times 0.8$ cm, and resolving structures down to 2 mm size. Gated studies provide almost motionless imaging of the heart and great vessels as well as the lower lung vasculature with CT-angiography that can surpass conventional studies. Due to the natural contrast between air and soft tissue, CT is ideally suited to imaging of the airway and lung parenchyma. However, an airway CT study is never solely a study of the airway alone but rather a thoracic CT optimized by design to highlight tracheobronchial imaging. Likewise diagnostic interpretation is not of the airway as an isolated structure but as a complex branching of conducting pathways with intimate relation to the distally connected parenchyma and to the accompanying lympho-vasular structures.

Although "helical CT and 3D imaging" have become part of the vernacular of ordering diagnostic studies it is important to appreciate what these terms mean so that they can be applied to best effect. All CT studies are comprised of three steps. They are: (a) data acquisition, (b) data post-processing and (c) data display. The physics of CT data acquisition is basically an extension of the principle of conventional radiography using X-ray photons to construct a density map of the body. From the first CT scanners introduced to clinical practice in 1972 until today, the basic mechanical process involves a patient moving through a gantry carrying a rotating source of imaging photons. After the patient body part has been scanned the density values encountered by the beam are translated into a series of electrical signals

that are mathematically formulated and interpolated to produce image slices for interpretation. The original scanners involved interrupted movement of the patient through the scanner while discrete slices were generated (conventional CT).

The first benchmark in CT advancement in the early 1990s was the increased speed provided by helical (spiral) CT that allowed for continuous patient translation during scan acquisition [7,8] to generate a volume of data [9–11].

The second major advancement was MDCT, which involves simultaneous acquisition of multiple slices during a single gantry rotation, resulting in faster translation of the patient through the scanner itself and faster processing of the data [3,4]. The general principles of MDCT appear straightforward. There are already multiple formats of MDCT from various vendors allowing for different processes of image acquisition. Newer scanning parameters offer a greater choice of user-defined imaging methods but scanning protocols must be carefully designed for the condition of interest. Failure to apply optimal imaging protocols at the outset will hinder further processing for interpretation and cannot be corrected retrospectively [12–14]. Therefore an important partnership must be built between the supervising radiologist acquiring the imaging data and the bronchoscopist with specific clinical questions in mind.

There are many and diverse implications for MDCT airway scanning, but perhaps of greatest importance has been the paradigm shift from standard 2D planar slices to routine 3D (volume) acquisition with high spatial and temporal resolution, and possible interpretations with alternate imaging perspectives that are independent of the original acquisition plane [15–17]. That is, through MDCT, the longitudinal axis (z-axis) resolution (e.g. looking at trachea in coronal), which is usually the limiting factor in airway 3D reconstruction, approximates the familiar and expected excellent resolution of the in-plane axis (x–y axis, looking at patient from below) [18].

Radiation dose is an important consideration during any chest imaging and good practice conforms to the principle of utilizing as low as reasonably attainable radiation exposure for acceptable image quality. Thinner slices to obtain noise-reduced images of superior diagnostic quality must be balanced versus the effort to limit patient exposure in milliamperes (mA) of dosage. If scanned with the appropriate protocol, additional 3D airway imaging does not require additional radiation exposure as the airway images are generated by software from the same data acquired for the chest imaging. Newer radiation dose modulation techniques have been incorporated into MDCT scanners to adjust dose to body habitus. There is also a move to use the natural contrast of the airway and lung to permit lower dose exposure [19].

Image post-processing and display: 2D, 3D and virtual bronchoscopic display

The airway morphology may be visualized using conventional planar 2D slices or 3D display [3,5,11,20–22].

2D display

Planar 2D axial CT remains the cornerstone of routine airway, lung parenchyma and mediastinal diagnostic imaging. It is the primary way to reconstruct the raw data and to provide a comprehensive review of the airway wall, caliber and patency as well as relationships of the airway with extrinsic structures such as hilar and mediastinal nodal structures, mediastinal and peripheral masses and regions of lung consolidation.

Much as with planar cine-fluoroscopy, planar CT can be used to guide and orientate bronchoscopes by confirming scope or sampling instrument positions. Bronchoscopic procedures performed in CT scanners can receive immediate interactive CT guidance of such procedures in so called Fluoroscopic-CT [23–30].

Multiplanar (MPR) and curved multiplanar reconstruction (CMPR) are simple variations of this 2D approach where the pixels (information building blocks) of data are reordered to an alternate imaging perspective that better serves interpretation. Examples would be sagittal or coronal views of the trachea [3,5,21,31]. The advantage of these planar approaches is that they require little additional computer power and are available for real-time interactive use on most scanner workstations without additional investment. The tissue

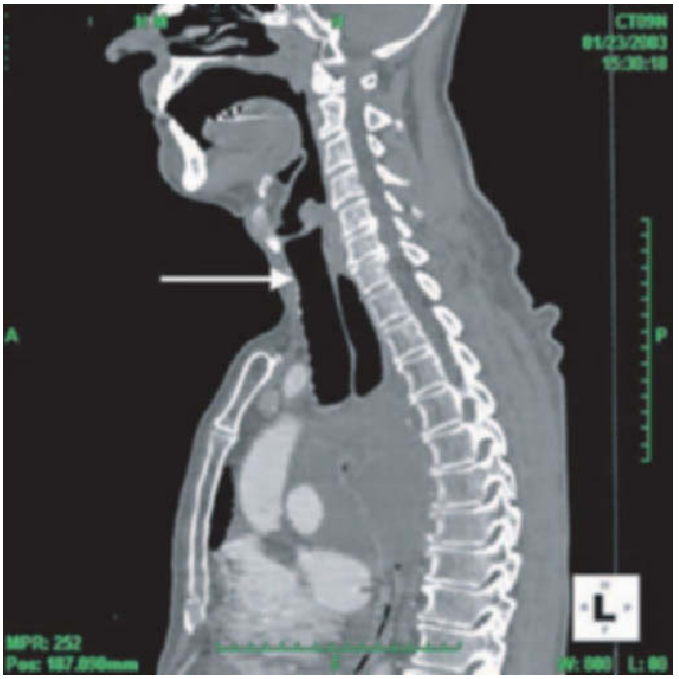

Figure 4.1 Normal upper airway. Sagittal MPR MDCT of trachea (arrow).

densities are the same as for routine imaging so lung parenchyma and mediastinal details are available. However, entire branching structures cannot be displayed in any single image. Although CMPRs can be constructed by defining a path along a bronchus of interest and this approach is helpful for an individual bronchus or clinical question, repeat paths must be drawn to perform a full bronchial evaluation. Slab editing (see Glossary) is used to produce images of diminished noise (Figures 4.1 and 4.2).

3D airway CT

The concept of performing 3D CT reconstruction is not new and 3D post-processing was investigated during the early era of CT scanning, but in the early days it was labor intensive and the results were adversely affected by reconstruction and motion artifacts that undermined their fidelity to the actual anatomy. Important advancement made possible with the latest generation MDCT scanners include rapid data acquisition and creation of voxels (volume elements) similar in size in all dimensions so that equivalent interpretative quality is now possible through an infinite number of planes and projections of high fidelity to the original data [6,32]. It is important to emphasize that although 3D images can potentially address specific clinical questions, they should never be interpreted in isolation or apart from the standard 2D axial study. Though the bronchoscopic perspective is a model for some 3D airway CT reconstruction, our vision of its role is broader than as a simulation tool as epitomized by VB or virtual endoscopy (VE). The optimal use of the CT data to interpret airway pathology involves an assimilation of all the information available regarding the lumen, the wall and extramural structures through the close interplay of planar and VR techniques specifically refined to the pathology of interest or of the planned therapy. We shall discuss later all the 3D approaches with specific attention to VR which is rapidly becoming the new standard.

Initial attempts at 3D CT used maximum intensity projection (MIP), minimum intensity projection (MinIP) or shaded surface display (SSD) which are techniques using only a portion (approximately 10–20%) of the data acquired to show select tissues of interest [21,22,31]. Modest computer

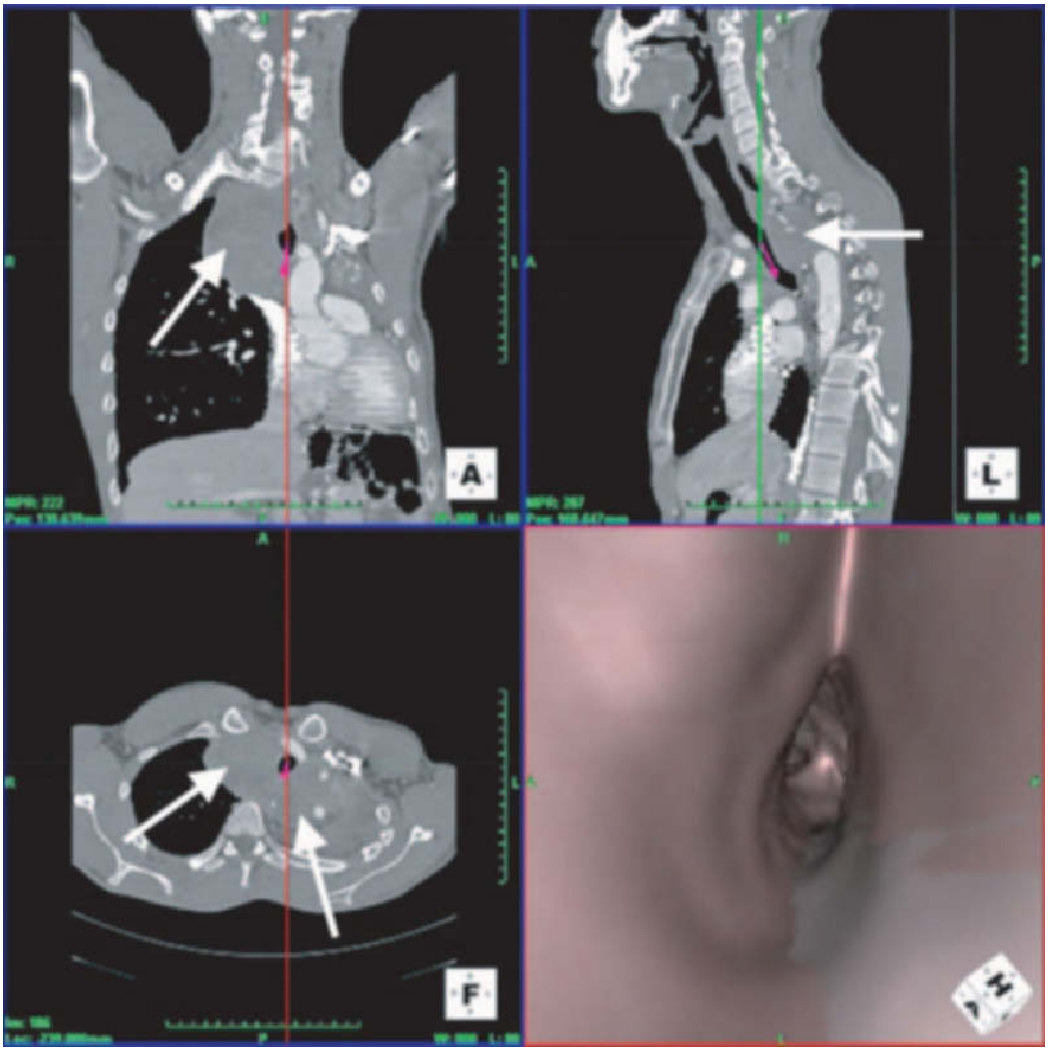

Figure 4.2 Mediastinal carcinoid. Soft tissue masses of tumor (arrows) compromise the trachea as seen by endobronchial perspective MDCT.

requirements are balanced by the limited information available. MIP displays only that portion of the study voxels with density values above a predefined value. It has been applied for nodule detection but has found little application in the air-containing tracheobronchial tree. MinIP displays only that portion of the study voxels containing density values below a predefined value [5]. It has been used to increase the conspicuity of areas of air trapping and can provide a crude representation of airway anatomy. In both MIP and MinIP, all the 3D information is reduced to a plane that discards depth information that can then only be appreciated through image movement. SSD displays only those voxels containing values that demarcate a surface border and it uses polygons and lighting models to generate an actual surface from slice images. SSD images do not require much computer power but may add editing difficulty when trying to remove the overlapping musculoskeletal structures of the chest. SSD had been largely applied to VB tools (see later) but other forms of 3D airway imaging have largely surpassed this approach [5].

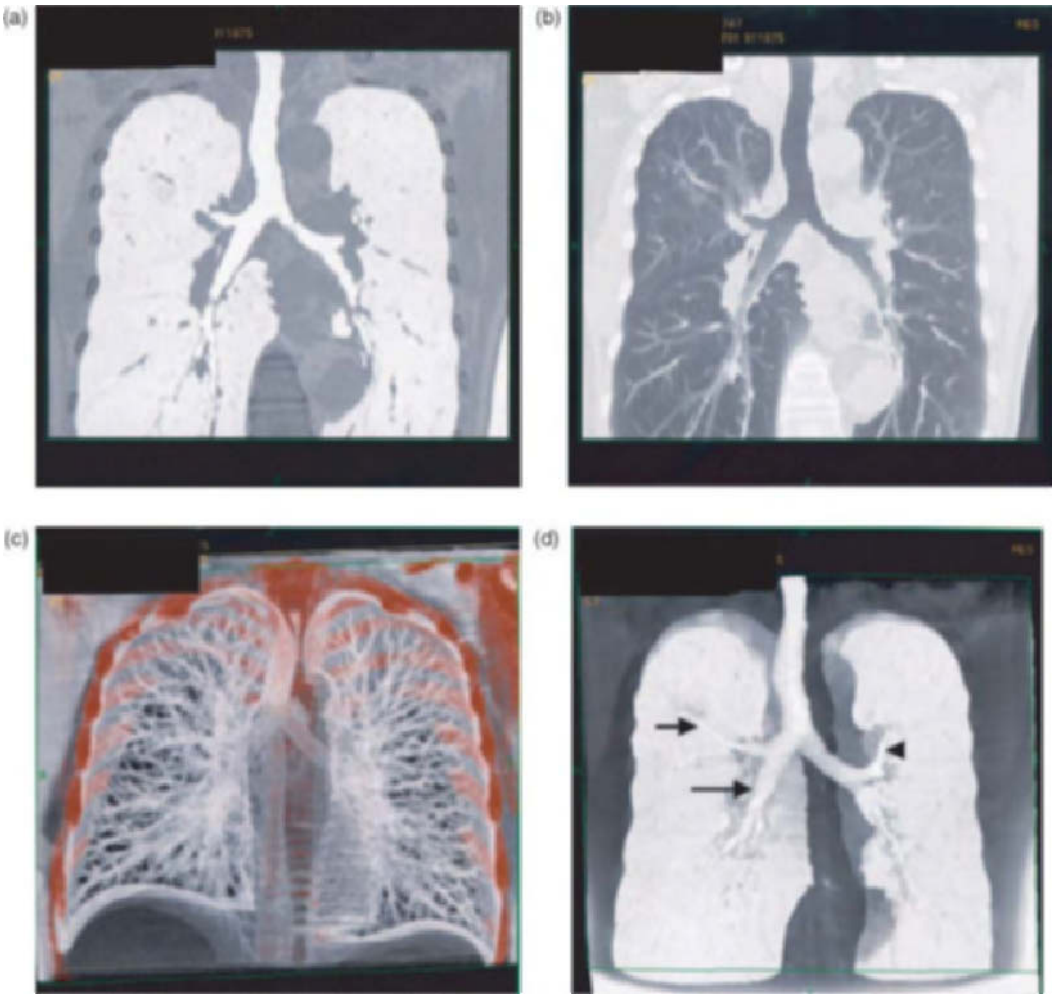

Figure 4.3 (a) Coronal volume rendered MDCT perspective with trapezoids to display the relationship of airway and mediastinal soft tissue. (b) Coronal volume rendered MDCT perspective with trapezoids to display the endoluminal perspective of airway. (c) Coronal volume rendered MDCT perspective with trapezoids to simulate conventional bronchography. (d) Coronal volume rendered MDCT perspective using edit planes to observe the right upper lobe bronchus (short arrow), right lower lobe bronchus (long arrow) and left upper lobe bronchus (arrowhead).

Volume rendering techniques represent the latest and most computer intensive form of 3D post-processing. They provide information of high fidelity in both spatial and density values when compared to the originally acquired datasets, so that the final 3D image preserves all the density values obtained such as airway lumen, airway wall, adjacent soft tissue and vasculature structures [5,6,22,33–35]. There are many different types of VR although they conform to the same basic principles of direct interpretation of the dataset without an intermediate step of surface description. VR requires a classification function (histogram of density values) to display tissues of interest (e.g. airway). The range of density values encountered in the chest may be manipulated through various opacity settings (trapezoids) to make structures visible and invisible, opaque and translucent [22,34]. Real-time, infinite variation of planes, projections and density values can be tailored to the patient's condition [33,36,37] (Figure 4.3a–c). Since interpretation is independent

of the acquisition plane select airways may be sought and displayed regardless of their orientation (Figure 4.3d).

Virtual bronchoscopy

A logical extension of the ability to generate 3D images is to connect sequential frames into a continuous motion sequence. VE has been most studied in the gastrointestinal tract where virtual colonoscopy has been validated to have a 75–90% sensitivity and 82–91% specificity for polypoid lesions greater than 1 cm [38,39]. Varied nomenclatures for VE of the airways have been introduced, including CT bronchography and virtual tracheobronchoscopy, but they will be considered under the more common acronym of VB [40–42]. Whether using the earlier MIP, MinIP or SSD or the currently preferred perspectiveVR, VB is a virtual reality tool to simulate the endoscopic perspective through post-processing of the CT data set [3,5,16,31,43–45]. All techniques ultimately produce a conical field of view to simulate the bronchoscopic perspective, and use animation tools to simulate the "fly-through" sensation (Figure 4.4a–d).

Fly-through or VB tools have perhaps caught the imagination more than any other 3D techniques, and yet have been slow to become widely applied or accepted. Until recently the fly-through approaches required very time-consuming editing tools before any simulation could be produced, and many computer systems lacked the computer power to generate a useful reconstruction in a timely manner. In addition, the nonaxial images were far inferior to the optimal in-plane axial planar slice resolution. However fly-through techniques have now become more user-friendly, the quality of the VB images improving and VB may ultimately be routinely applied with a real-time interface that preserves spatial relationship and allows direct or automatic navigation through a center line [10,12–14,42,46–49]. Using MDCT, the peripheral airways extending to just short of the pleura may be imaged. The ability to sample small peripheral lesions will be discussed in further detail in a section to follow.

Despite its name, the future of VB of the airway is not as a substitute for fiber-optic bronchoscopy, but rather as a distinct extension of the lung CT technique that gives select benefits derived from its endoluminal perspective. VB is a noninvasive tool that gives a faithful representation of caliber, contour and orientation as well as some unique perspectives with an assimilation of internal and external relationships [42,50,51].

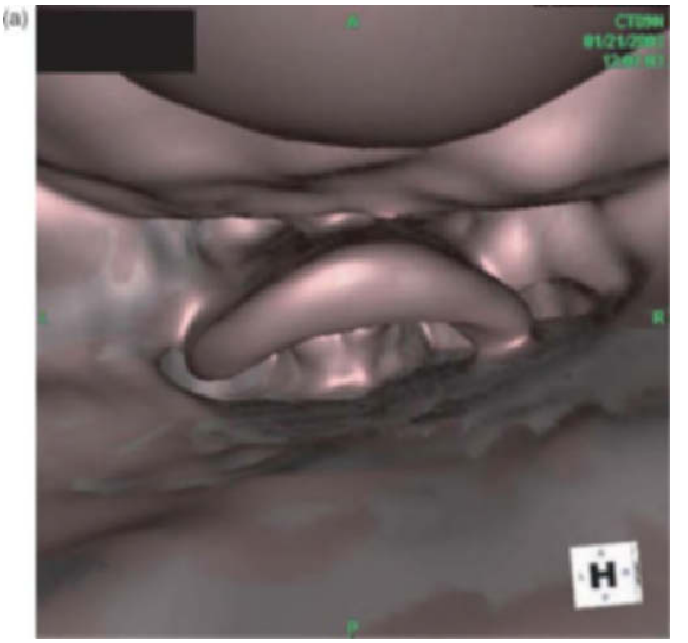

Figure 4.4 (a) Virtual bronchoscopy. A view of the epiglottis.

It may have a role in pre-procedure planning, intra-procedural guidance or in procedural training [52]. The advantages are counterbalanced by radiation exposure, nondynamic studies and a lack of information on hue, indurations and small mural infiltrations [46]. The optimal value of VB is when it is used with other scan information available from within the wall and beyond to the lung periphery. 3D planar maps are a useful adjunct to give precise correlation of the endoluminal anatomic localization within distal branches of the bronchial tree or to plan transbronchial biopsy approach for fine needle aspiration. Planar and VR images are preferred for measurement accuracy due to distortion inherent in endoscopic perspective simulation. Optimal value is gained when such VB studies are discussed in direct consultation between radiologist and pulmonologist.

Functional airway CT

In addition to providing multiplanar and 3D representations of airway pathology, and in guiding the bronchoscopist to a peripheral airways segment, the rapid helical CT (HCT) has a third significant role – that of providing data on the functional

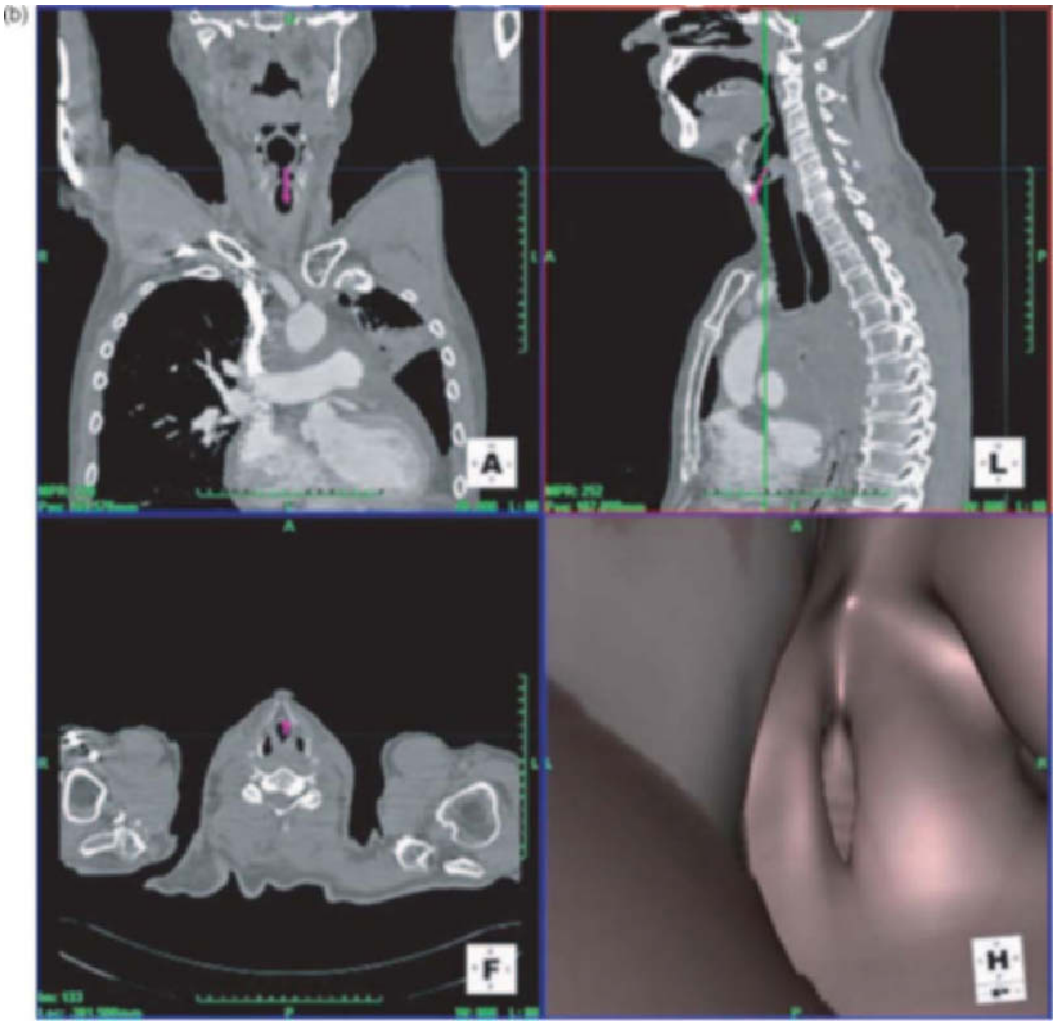

Figure 4.4 (b) Virtual bronchoscopy. Right lower image: an endoluminal view of the underside of the cords. Axial, coronal and sagittal MPR views at the same level.

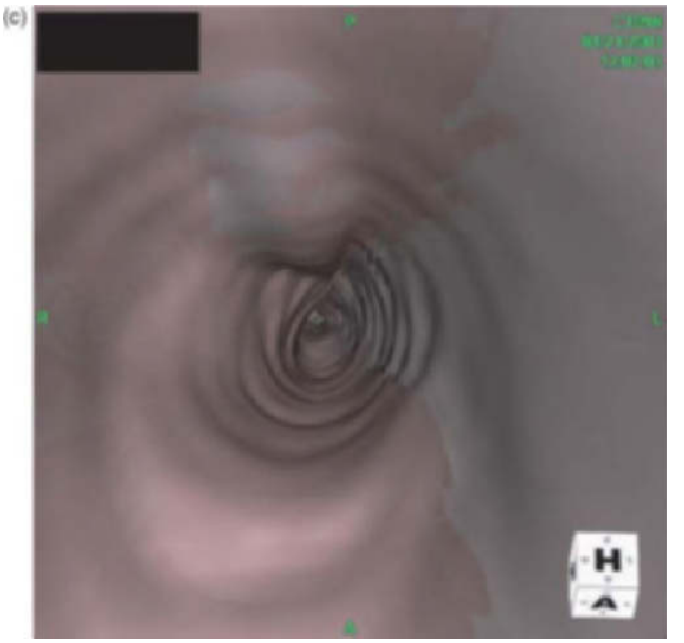

Figure 4.4 (c) Virtual bronchoscopy. An endoluminal view of the trachea.

correlate to structural abnormalities seen in the normally static views of the axial CT images. The normal lung parenchyma has a fairly homogenous density made up of the secondary pulmonary lobules. An imbalance of ventilation and perfusion can cause regional variation in density values that can be used as a measure of lung disease and gas exchange. By comparing such attenuation patterns in images taken during both inspiratory and expiratory phases, an indirect measure of air trapping may be gained [53–56]. CT can show air trapping even when PFTs are normal and a score may be calculated based on the area involved compared to normal lung and which correlates with the degree of airway obstruction [57,58]. A comparison of 2D versus 3D post-processing of inspiratory and expiratory HCT reveals generally good correlation ($r = 0.89$) with static lung volumes on pulmonary function testing (PFT). The 2D approach gave a slightly smaller estimate of lung volume (mean 3.6%) than the 3D technique, which is preferred for the estimate of lung volumes [59]. Qualitative visual scoring and quantitative computer based scoring systems have been shown to correlate well with nuclear ventilation perfusion studies for the planning of segmental lung volume reduction surgery (LVRS) in emphysema patients also [60]. Combined with VB guidance, functional airway CT may guide the interventional bronchoscopist in the future in performing directed bronchoscopic LVRS [61,62].

Airway magnetic resonance imaging

Magnetic resonance imaging (MRI) is not frequently applied to airway morphologic imaging. MRI operates on the principle that the moment of spinning protons within tissues may be affected by radiofrequency pulses and these same tissues will also emit radiofrequencies characteristic of the tissue type as a result. Its advantage lies in the lack of ionizing radiation and in its multidimensional capabilities [63]. However, it is relatively time consuming and applications for anatomic airway imaging is limited due to the lack of conventional hydrogen in the airways to generate signal. The poor signal in air containing structures results in suboptimal contrast resolution. In addition any metal (e.g. surgical clips or metallic and alloy airway stents) within the region of interest causes significant "blooming" artifacts that significantly degrade image quality. As always, patients with pacemakers are contraindicated for study and those with significant claustrophobia may also present difficulties. Image sequences are designed to gather the data

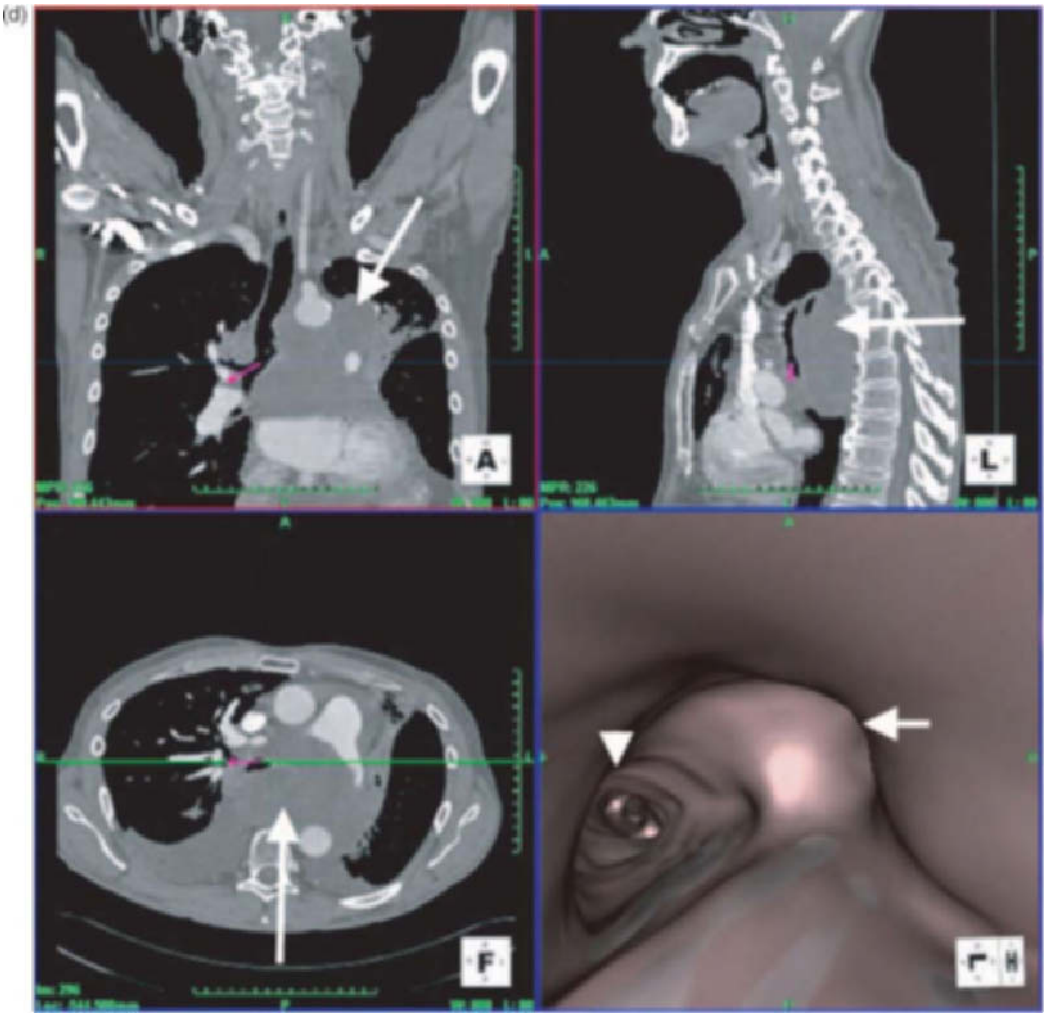

Figure 4.4 (d) Virtual bronchoscopy. An endoluminal view with navigation toward the right lower lobe bronchus (arrowhead) and showing the right upper lobe take off (short arrow). On the accompanying MPRs mediastinal lymphadenopathy is observed (long arrows).

in 2D or 3D [64]. The former permits slice thicknesses as small as 3 mm whereas the latter can provide an increased number of slices constructed of isotropic voxels of high spatial resolution. Combined with MR angiography, accurate information on bronchovascular relationships can be provided.

Hyperpolarized noble gas diffusion imaging

Magnetic resonance imaging may have more potential through some of its unique capabilities for imaging molecular agents, which may be developed into a form of functional imaging as well. Hyperpolarized noble gas diffusion imaging of the lung remains within the research realm at the present time, but it clearly has potential for structural and functional imaging of obstructive airway disease. Nuclear medicine already provides information on lung ventilation (xenon 127 or 133 or krypton 81) and perfusion (technetium 99m labeled agents) but lacks the spatial resolution for anatomic detail. Noble gases such as helium 3 or xenon 129 are chemically inert, non-radioactive gaseous compounds, which are

magnetically hyperpolarizable using laser before they are administered to the subject. After inhalation, the inhaled gases that traverse the airspaces of the lung during a breath hold, can be statically and dynamically analyzed by MRI. MRI can "label" individual molecules of noble gas and provide an indirect measure of their diffusion, measured in apparent diffusion coefficient (ADC). In regions of large airspaces such as areas of emphysematous destruction, the ADC will be large whereas it will be smaller in areas of more restricted movement, thus providing a measure of peripheral lung architectural distortion. An inverse relationship has been found between these indices and with the percentage forced expiratory volume in 1 s (FEV_1), and the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) [65–67]. By measuring the decline in noble gas polarization through interaction with oxygen molecules, regional *in vivo* oxygen concentrations can be measured [68]. It has also been suggested that certain sequence changes in MRI signal after inhalation of 100% oxygen reflect regional differences in DLCO [69]. Much more work needs to be done to validate these findings and to accurately assess their relation to lung geometry and function before routine clinical use of these agents can be prescribed.

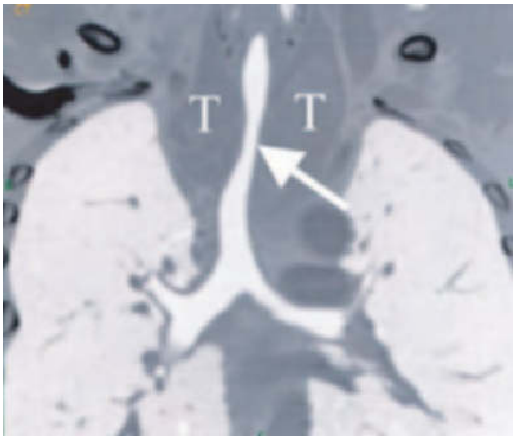

Figure 4.5 Tracheal compression (arrow) secondary to a large substernal goiter (T).

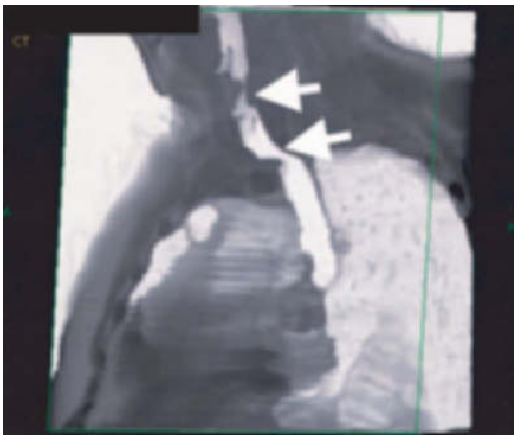

Figure 4.6 Tracheal distortion and narrowing secondary to keloid formation (arrows).

Clinical applications of 3D multiplanar CT reconstruction and VB

Airway caliber change

The most common reason for referral for 3D imaging is the evaluation of compromised airways with stenosis due to an infiltrating process, fibrotic process, or extrinsic compression. Most case series of 3D CT-imaging of central airways narrowing list malignancy as the majority cause. This includes both primary bronchogenic carcinomas as well as metastatic diseases from esophageal and thyroid primaries amongst others. Increasingly, descriptions of a broad range of benign conditions are listed as well. These post-infectious and inflammatory processes include: post-intubation and tracheostomy stenosis, lung-transplantation anastamotic stenosis, mycobacterium (especially Mycobacterium tuberculosis) associated scarring, Wegener's granulomatosis, airway amyloidosis and caustic ingestion. Benign causes of extrinsic compression studied by 3D CT imaging include: thyroid goiters, aortic aneurysm and mediastinal fibrosis [40,70–73] (Figures 4.5 and 4.6). The negative and positive predictive values of airway CT imaging for airway stenosis are very high when the full range of 2D and 3D processes are applied [22,74]. Though routine axial planar CT performs well, subtle tapering of airways, aberrant take-off of segmental bronchi, discrete web-like compromise and narrowed airways that run oblique to the imaging plane may be missed with conventional

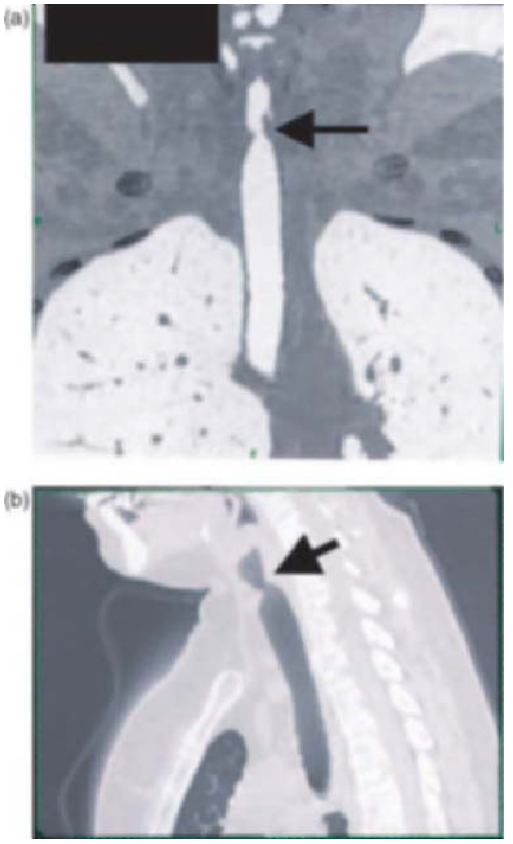

Figure 4.7 Tracheal web. (a) A coronal volume rendered MDCT demonstrates a discrete web in the trachea (arrow). (b) A left sagittal volume rendered MDCT demonstrates a discrete web in the trachea (arrow).

axial review [34,35,51,74–76] (Figure 4.7a,b). Positional dependent causes of airway compression and collapse may be missed even during bronchoscopy, but may be visible in a VB of the upper airways [70]. Dedicated 3D images are constructed to provide accurate detail of the site, length, character and multiplicity of stenosis, as well as information to map the stenosis with respect to the bronchoscopic perspective [77–79]. At a minimum, a series of 2D planar coronal and sagittal reconstructions though select planes parallel to the airway of interest are required to fully evaluate stenosis. The preservation of the integrity of the airway wall versus endobronchial invasion may be inferred by analysis for any irregularity that may suggest infiltration.

Comparative studies in this fast-evolving field are often difficult to interpret and compare because the technology described in one paper is often no longer applicable the next year or is comparable to what is available today. A 1996 study of 64 patients with obstructive central airway lesions by Remy-Jardin and colleagues found axial CT and multiplanar reformation to be 99% accurate and superior to 3D reconstruction by SSDs and MIPs with accuracies of 90 and 81%, respectively. It is worthy to note that these latter techniques are left largely obsolete by advances in VR [80]. Kauczor and colleagues report a 95% accuracy in the diagnosis of airway stenosis, with 100% accuracy in the central airways but with missed lesions in segmental airways [51]. Likewise, Ferretti and colleagues published in 1997 findings of similar high (95%) sensitivity in VB detection and quantification of 39 out of 41 stenotic segments in 29 patients when compared to follow-up bronchoscopic examination. Mild stenosis, of less than 25% reduction in the tracheobronchial lumen was missed, but detailed VB can be generated out to the fourth generation bronchi [76]. Fleiter and colleagues also in 1997 found that VB of diagnostic quality was achieved in 95% of 20 lung cancer patients; however, whereas high grade stenosis was well characterized by VB and comparable to bronchoscopy examination, discrete tumor infiltration and extraluminal impression were missed in 25% of the patients [46]. In a study a year later in 1998, improved 3D reconstructed VB and 2D axial CT slices were found to be equally accurate when directly compared to bronchoscopy in denoting the location and length of the stenosis; VB provides a better gauge of the degree of stenosis which tends to be underrated on axial CT slices, conversely mucus plugs simulating additional airway lesions may be over diagnosed [81]. In a study of anastamotic complications in lung-transplant recipients, VB is slightly more accurate than axial CT in the diagnosis and length estimate of stenotic lesions, however the differences are not statistically significant. Furthermore VB missed dehiscence and could not of course diagnose infections or their etiology [72]. It is in general easier to diagnose or infer causation of airway narrowing in malignancies, whereas in a study of 28 patients with only benign causes of airway stenosis, the addition of 3D VR only increased

the diagnosis made by axial CT alone from 70 to 78% – a nonsignificant improvement [40].

One of the principles of successful airways intervention is the goal of restoring lung function rather than simply reopening an occluded segment of airway, whether by removal of obstructing endobronchial lesions or by stenting opening extrinsic compression. When high grade stenosis or complete occlusion are present, a pre-procedural review of the axial and 3D reconstruction of the lung parenchyma distal to the site of obstruction can indicate whether there is functional lung tissue present and may improve the estimate of the likelihood of re-expansion after bronchoscopic intervention [51,81]. A contrast enhanced CT scan for the evaluation of the pulmonary vasculature is especially helpful in this regard, to avoid performing potentially risky procedures only to reopen non-perfused dead space (Figure 4.8).

Through reproducible 3D perspectives, repeatable consistent and accurate measurements of the temporal change of airway caliber may be a better guide as to when follow-up bronchoscopic examinations are needed and hence obviate frequent "surveillance" airways examinations and premature interventions [51,81]. This is particularly true for patients with benign chronic inflammatory conditions such as Wegener's granulomatosis, post-intubation granulation or lung transplant stenosis at the anastomosis [72,73,82] (Figures 4.9 and 4.10a,b).

Suboptimal 3D VB image quality are commonly due to several factors. Inability to breath hold for the scan cycle, especially in patients with impaired respiratory function, results in motion artifacts in 2–3% of cases [34,40]. Strong cardiac pulsation has also prevented evaluation of 3D reconstruction [46]. Reduction in unwanted motion artifact may be achieved by deliberate hyperventilation for a minute pre-scan, and by the introduction of MDCT with shorter scan times [40]. Volume artifacts and stair-stepping artifacts can be reduced by thinner sections and by overlapping sections, respectively [51]. Beyond technical considerations of the reconstructed images, 3D VR and VB have some limitations in elucidating causes for upper airway obstruction, these include causes for vocal cord dysfunction, and missing about one half of glottic webs and laryngotracheomalacia in studies constructed from a single position breath hold

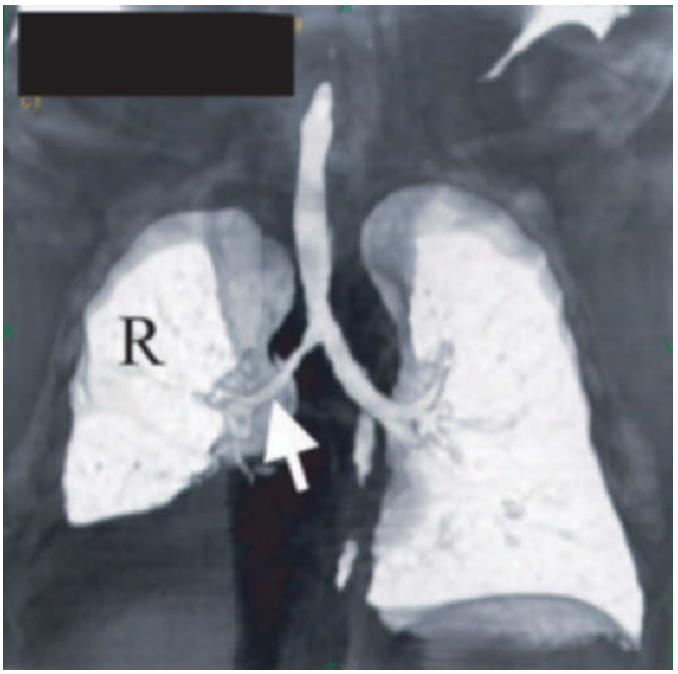

Figure 4.8 Recurrent adenocarcinoma of the right hilum causes high grade narrowing of the bronchi (arrow) with secondary right lung volume loss seen by VR MDCT.

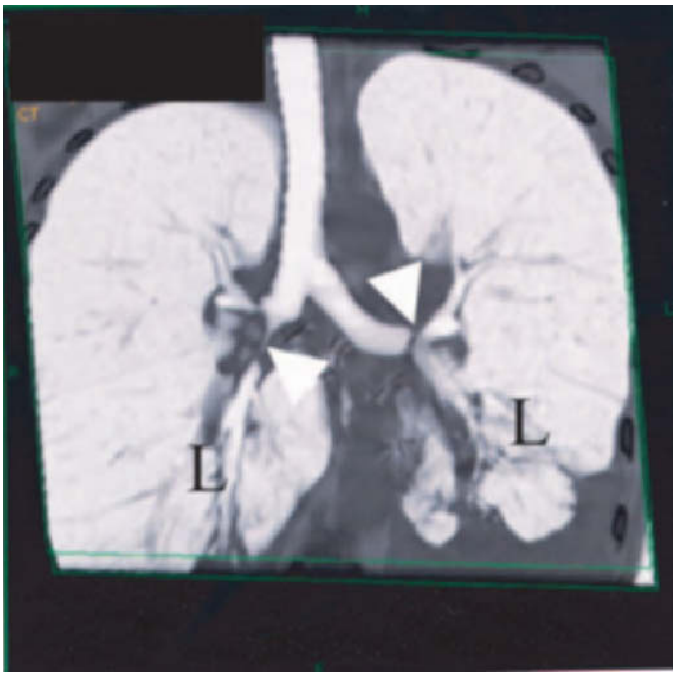

Figure 4.9 Bilateral bronchial anastamotic strictures after lung transplant (arrows) are associated with lower lung volume loss (L) seen by VR MDCT.

study [77]. Occult tracheobronchomalacia may be a cause of unexplained dyspnea or chronic cough, and may reach as high as 5–10% of patients with chronic pulmonary complaints, with the incidence increasing with age [83,84]. Tracheobronchomalacia has heretofore been found incidentally during diagnostic bronchoscopy, with the observation of dynamic airway collapse, or by cine fluoroscopy when there is a clinical index of suspicion of this disorder [85]. Dual study inspiratory and expiratory imaging for expiratory collapse can reveal various forms, locations and severity of tracheobronchomalacia noninvasively, but it should be used judiciously and only when there is a clear clinical indication of management benefit due to the doubling of radiation dose required for such studies [74,83]. As noted, retained secretions may be erroneously interpreted as false positive endobronchial airway lesions.

The diagnosis of bronchiectasis can now be made noninvasively by normal to high resolution CT without the need for bronchography or airway examinations. Bronchiectatic changes are easily discerned on high-resolution axial planar imaging, with the classic finding of a segmental bronchi larger than its accompanying pulmonary artery. Similarly the character (tubular or saccular) and the extent of mucus plugging within these bronchiectatic segments may be documented. There is some suggestion that a link may be made between morphologic CT features (wall thickening, extent and lung parenchyma density) and clinical activity [86]. Multidimensional CT is applied to segmentally map focal bronchiectatic change (e.g. post-inflammatory) for consideration of segmental resection. It is easier to appreciate the whole lung distribution of bronchiectatic change using coronal and sagittal planes and this may have a role in better quantifying changes over time or response to therapy (Figures 4.11 and 4.12).

Airway stenting

Two-dimensional multiplanar and 3D reconstruction of airway pathology and its relationship to adjacent structures are very helpful adjuncts in the planning and follow-up for airway interventions. A prospective candidate for airway stent placement should ideally be initially imaged to aid in the planning for stent placement [87–89]. During such studies, 2D and 3D images are

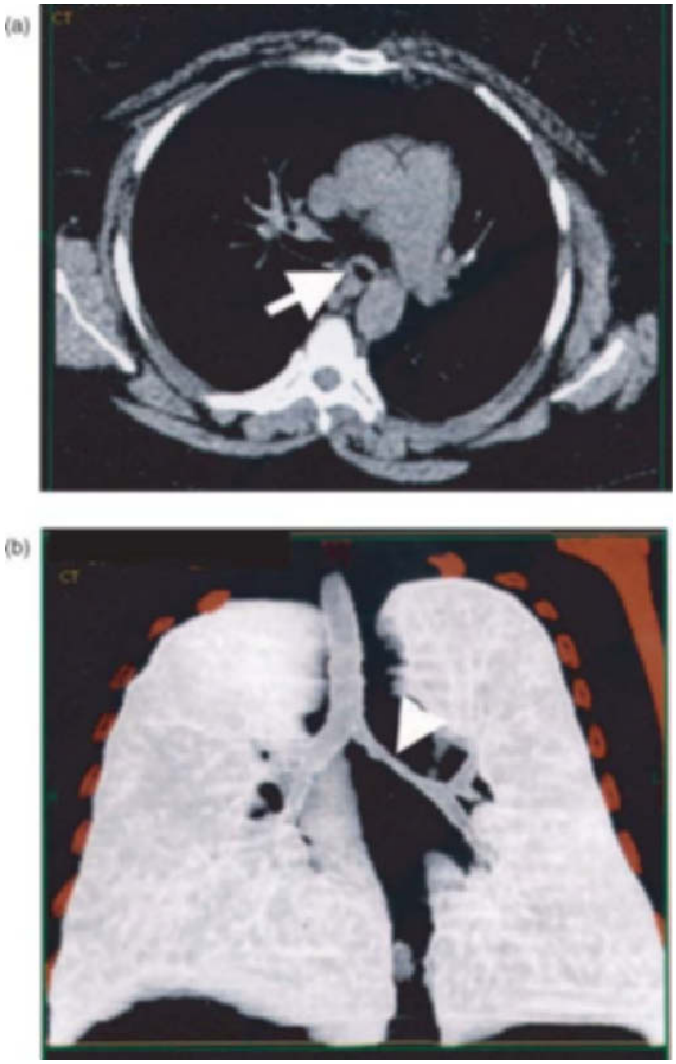

Figure 4.10 Wegener's granulomatosis. (a) Circumferential thickening of the left lower lobe bronchus (arrow) is seen on conventional axial planar MDCT. (b) The full extent of airway compromise (arrow) is perceived using VR MDCT.

reviewed to better appreciate the etiology of stenosis, location and extent of stenosis, as well as the optimal bronchoscopic approach [89]. (Figure 4.13a,b). The stent components may be designed and tailored to the individual patient using measurements taken from such studies that are more accurate than axial imaging alone (Figure 4.14a,b). The CT can show the area of airway compromise and its site can be measured from recognizable bronchoscopic landmarks e.g. glottis or the carina to aid in selecting appropriate airway coverage of the lesion. Volume rendering is the preferred method for CT imaging as it preserves the contrast resolution of the stents, airway, lung and other mediastinal structures, and it minimizes metallic artifact. VR CT has been useful to assess stent performance (Figure 4.15) including complications of caliber change and migration. Tumor encroachment or areas of granulation tissue may be documented for revision and re-expansion of lung may be accurately assessed after placement (Figure 4.16). It has a role in the noninvasive assessment of those in need of stent salvage or replacement as 3D approaches allow greater reproducibility for longitudinal follow-up of stent caliber change or migration (Figure 4.17).

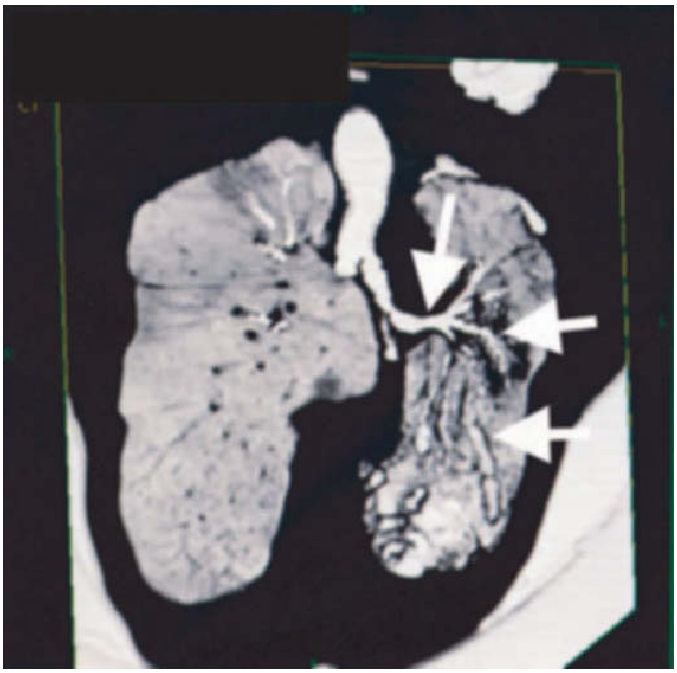

Figure 4.11 Bronchiectasis. VR MDCT is used to highlight saccular traction bronchiectasis (arrows) in a shrunken fibrotic left lung.

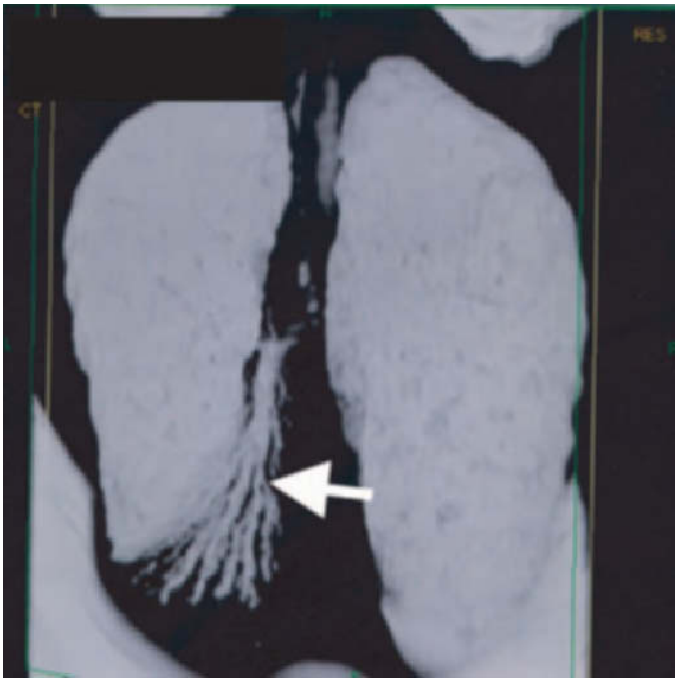

Figure 4.12 Focal bronchiectasis. VR MDCT with an anterior perspective demonstrates a localized area of post-inflammatory bronchiectasis (arrow) that may be suitable for resection.

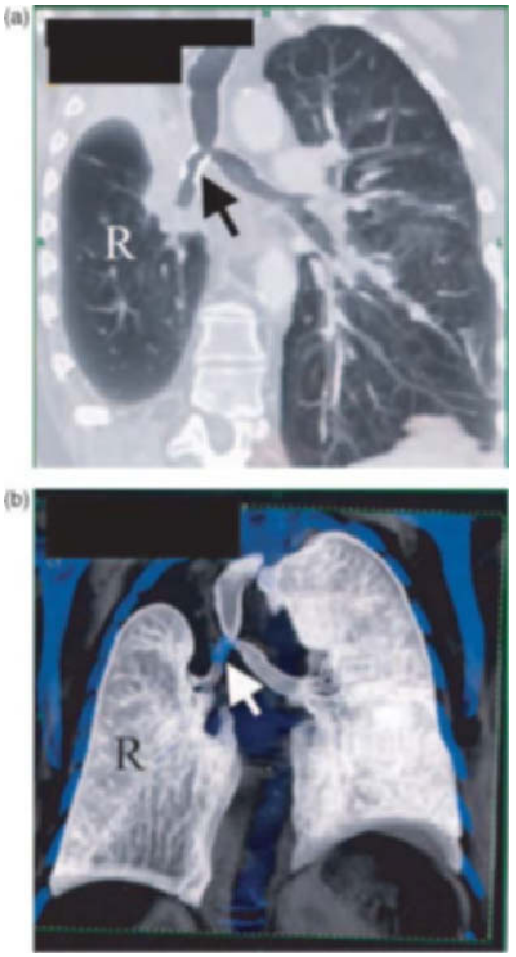

Figure 4.13 (a, b) Stent. Two VR MDCT views of a stent placed (arrow) to maintain airway patency in the face of recurrent hilar tumor encroachment. Note the right lung volume loss (R).

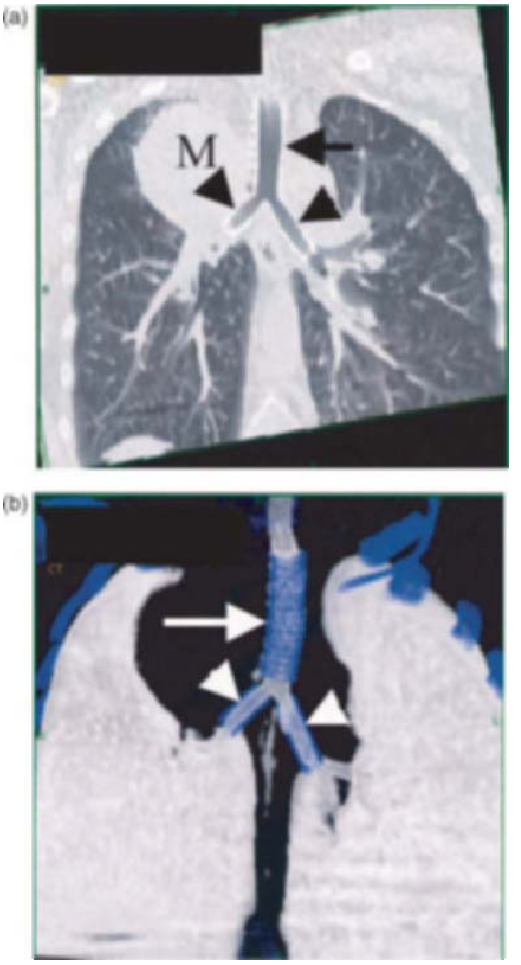

Figure 4.14 (a, b) Stent. Two VR MDCT renderings. In this patient with a large right upper lobe tumor mass (M) a Y stent in the tracheal (long arrow) and mainstem bronchi (arrowheads) was placed to prevent airway collapse and is illustrated using VR MDCT.

Focal lesions

Proximal lesions

Axial CT has high sensitivity for the detection of focal filing defect lesions within the airway, whether they are primary to the tracheobronchial tree or secondary to local invasion of an extrinsic process (Figures 4.18 and 4.19). An endobronchial process must always be excluded in the setting of segmental or lobar collapse found on CT or chest radiograph. Most neoplastic lesions involve secondary invasion of the airway by a medial lung lesion or adenopathy and primary lesions are less commonly observed or visualized within collapsed bronchi. Neoplastic processes tend to have a characteristic mass-like character, which may obscure known tissue boundaries. CT has poor specificity for characterization of discrete small endotracheal or endobronchial lesions and benign or malignant processes are hard to differentiate from a pseudomass of mucus on a single study. Unlike in virtual colonoscopy where there is an established bowel prep to clear out the colon, there is no agreed upon respiratory preparation with bronchodilators or manual percussion and drainage or intermittent positive pressure breaths (IPPB) clearance even in

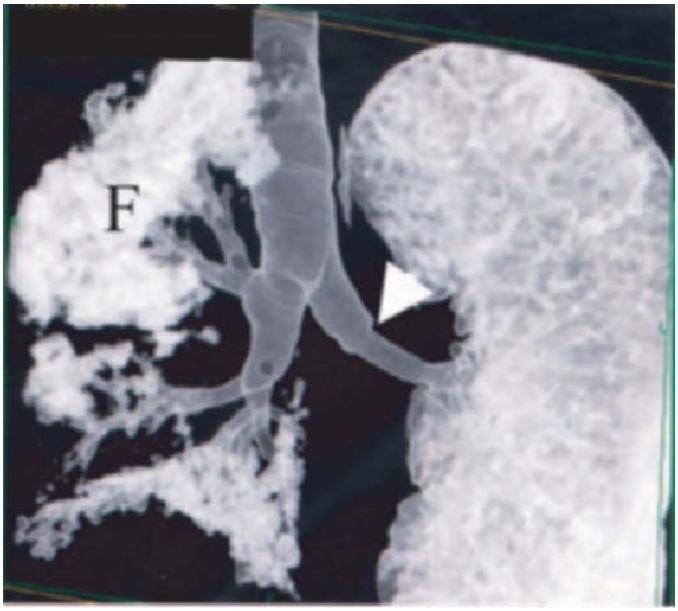

Figure 4.15 Stent. Follow-up VR MDCT of this transplant patient demonstrates a widely patent left bronchial anastomosis after stent placement (arrow). A fibrotic right native lung (F) is noted.

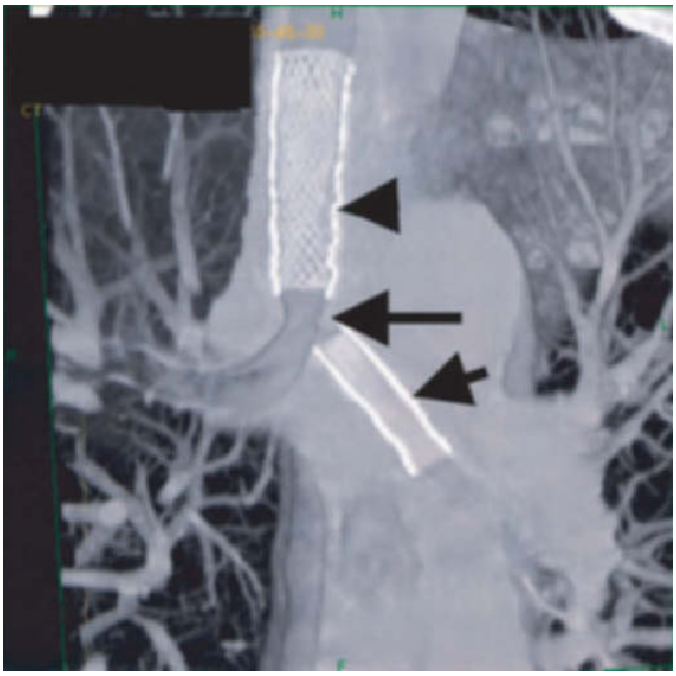

Figure 4.16 Stent. A tracheal stent (arrowhead) and left mainstem bronchial stent (short arrow) were placed in this patient with strictures secondary to acid inhalation. Granulation tissue encroachment over the left mainstem bronchus (long arrow) is observed on this coronal VR view.

established chronic bronchitics about to undergo scanning for a VB. Repeat scanning after expectoration or change in posture may help, but this will entail added expense and radiation exposure. Reconstructed CT images are applied to help decide the feasibility of primary resection through evaluation of the longitudinal extent of tumor and the anticipated amount of remaining trachea

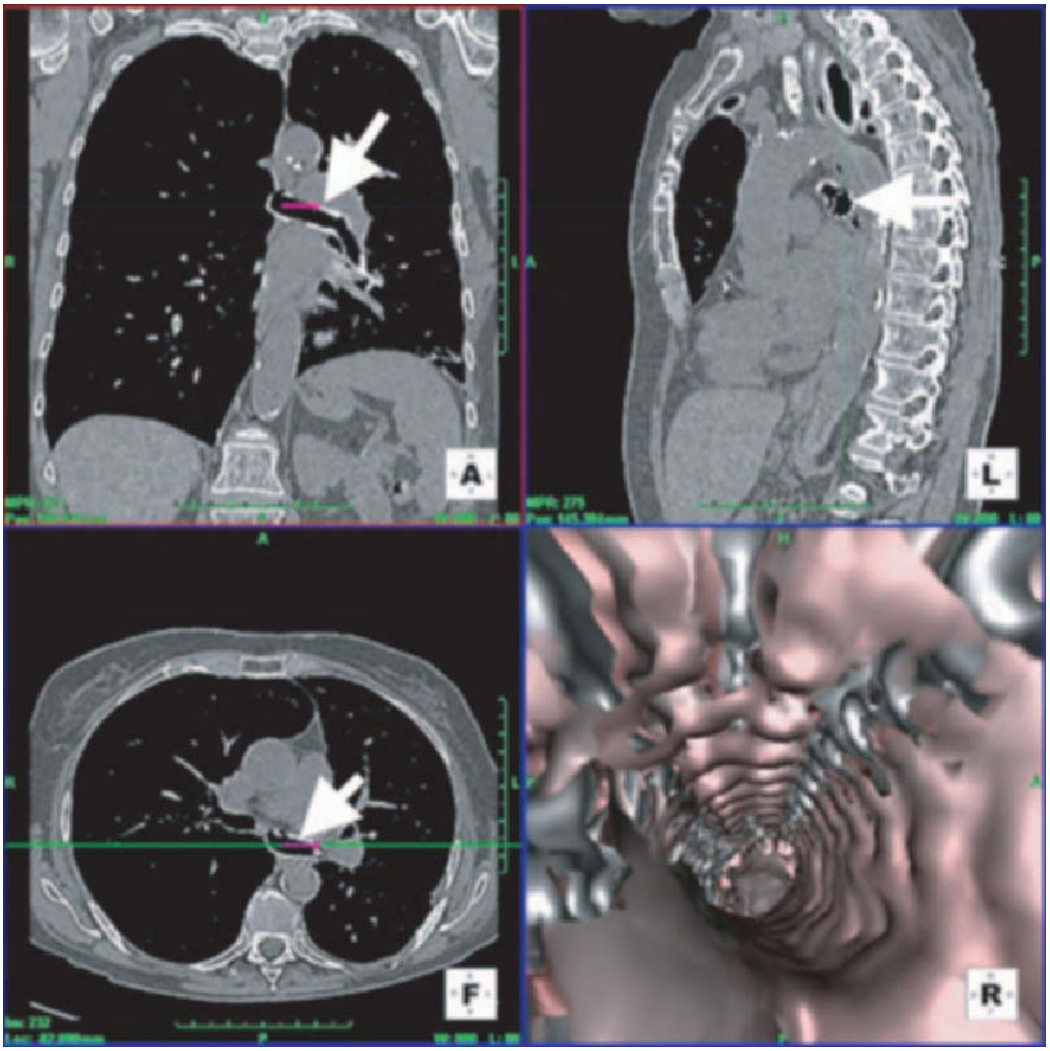

Figure 4.17 Stent. A VB and MPR review of a left mainstem bronchial stent (arrow).

for anastomosis. Dedicated 3D measurements aid conformal radiation port planning and palliative airway tumor debridement and stent placement [34,35,74,90–92] (Figure 4.20a,b).

Peripheral lesions

Planar cine-fluoroscopy has been used and remains the mainstay of real-time guidance in bronchoscopic tissue sampling of endoscopically invisible lesions; these include primary lung cancer, metastatic cancers and benign lesions [93–95]. The success of fluoroscopic guidance is however dependent on the accessibility to the lesions and their visibility on fluoroscopy, with the yield generally lower for more peripheral and smaller lesions, i.e. those lesions greater than 4 cm from the inlet of a segmental bronchus, and those lesions below 2 cm in diameter. On average these less favorably disposed targets yielded a diagnosis on bronchoscopy of 15–50% versus more than 60% for more central and larger lesions [94,96–99]. The introduction of CT has vastly expanded anatomic information for pre and intra-bronchoscopic evaluation. Axial image review may suggest the ideal bronchus to approach for transbronchial bronchoscopic biopsy [96], or preferentially suggest a percutaneous

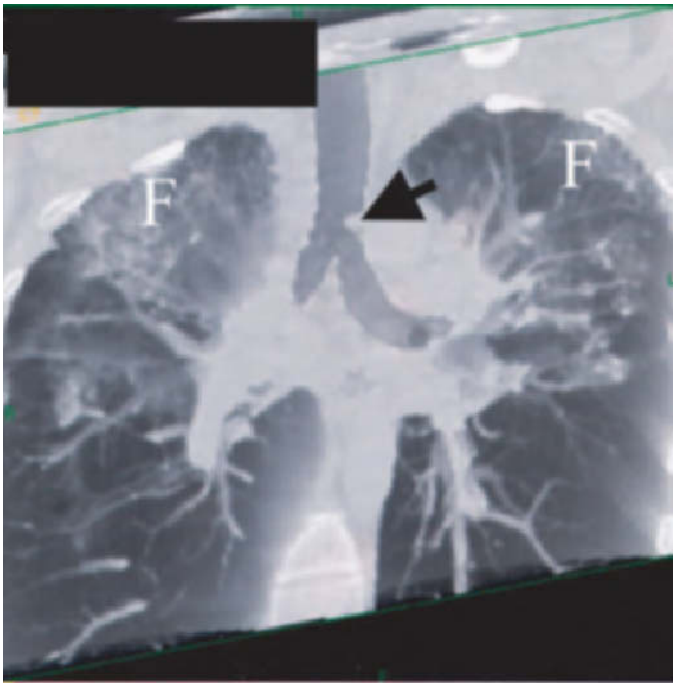

Figure 4.18 Polyp. Tracheal polyp (arrow) on VR MDCT. Incidental note of bilateral upper lung fibrotic change (F).

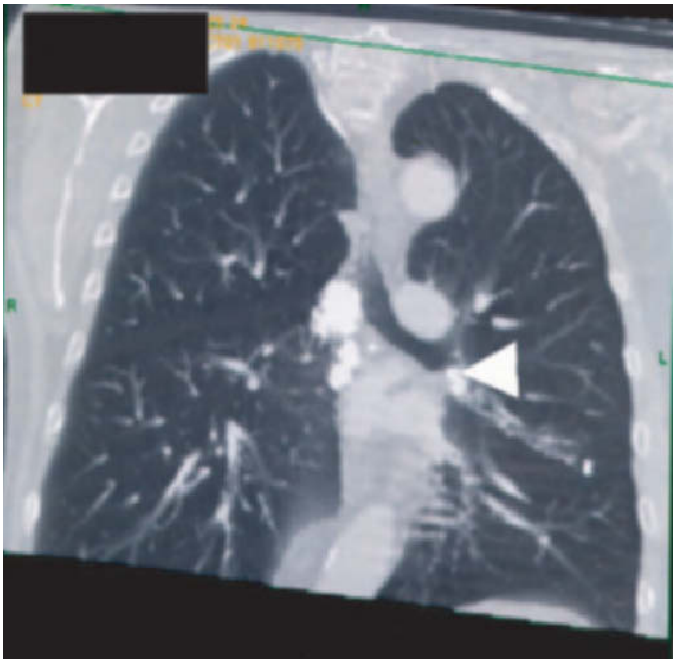

Figure 4.19 Broncholith. A broncholith was seen using VR MDCT eroding into the bronchus of the left lower lung (arrow) in this patient with granulomatous lymphadenopathy.

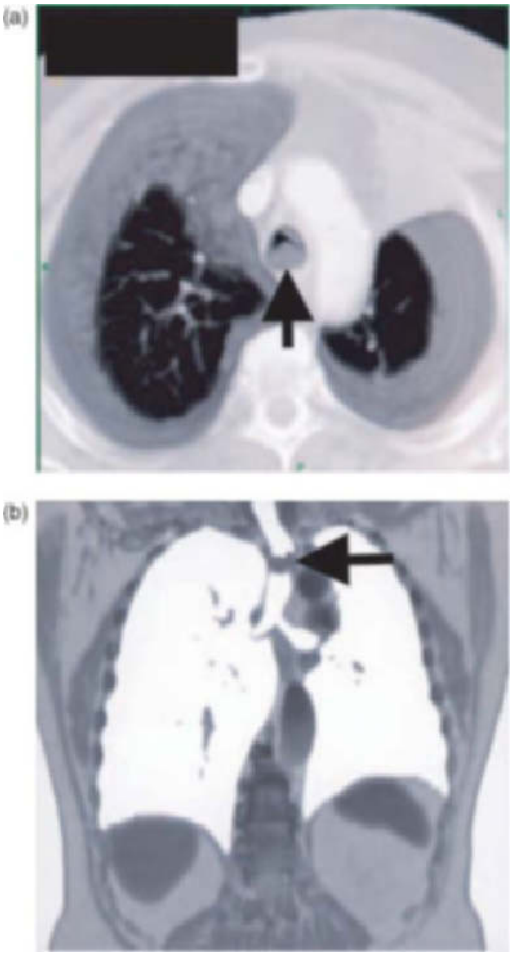

Figure 4.20 Squamous cell carcinoma. A focal primary squamous cell carcinoma in the mid trachea was seen as a filing defect (arrow) on coronal view using VR MDCT and a superior perspective.

approach [100]. Bronchoscopies have been performed in the CT scanner for improved yield in the diagnosis of bronchoscopically invisible lesions, although the majority of cases have been for mediastinal or hilar lymph node sampling rather than for peripheral lesions [25,26,28–30,101]. Although labeled as "Fluoroscopic" CT scanning, in many instances, the images are obtained not in real time as the bronchoscope is being advanced, but rather in stop sequences to confirm the position of the sampling needle or forceps [25,26,28–101]. In one series where CT fluoroscopy was used to guide the sampling of peripheral lesions, diagnostic yield remained at 67%, because of the bronchoscope and biopsy instruments' inability to reach the target lesion [30].

As previously noted, MRI has so far had a more limited role in the diagnostic imaging for thoracic diseases. The development of open-configuration operating magnetic resonance (OCMR) units has given rise to the possibility of performing procedures under direct MR guidance. While OCMR have been used successfully in the area of neurosurgery and in directed biopsies and therapies of hepatic, prostate and other organs, there has been no practical application in diagnostic and interventional bronchoscopy, in part because of the incompatibility of bronchoscopic instruments within a strong magnetic field [102–108].

The parallel development of 3D VR and the introduction of smaller caliber "ultra-thin" bronchoscopes are changing the ability to sample with greater accuracy smaller and more peripheral parenchymal lesions. Thin and ultrathin bronchoscopes were originally designed with pediatric airways in mind, but although fine in caliber with outer diameters between 1.8 and 2.7 mm, the earlier instruments lacked a biopsy channel and hence were limited to observational purposes only [109,110]. Tanaka *et al.* [111–113] extended the application to the examination of peripheral airways pathology in adults and in the mid-1990s, together with Hasegawa, introduced a 2.7-mm ultrathin bronchoscope with a 0.8 mm operating channel. The current generation of these thin and ultrathin bronchoscopes have an outer diameter between 2.2 and 3.6 mm, versus the standard adult diagnostic bronchoscopes measuring between 5.0 and 6.3 mm. Their smaller dimensions permit the examination of between four to seven more airway generations than achieved by standard bronchoscopes [23,114,115]. Early results are encouraging, with some peripheral lesions directly visualized, and others biopsied under fluoroscopic guidance; an overall diagnostic yield of 11 out of 17 patients (64.7%), with no diminished yield for lesions less than 3 cm, 7 out of 10 (70%) was achieved in one series [115]. Even greater accuracy can be achieved with CT guidance for very small lesions less than 2 cm; the ultrathin bronchoscope could be guided to 20 out of 23 patients' lesions, with an 81.8% sensitivity for diagnosing lung cancer, and only a slightly lower rate of 77.8% for benign lesions [23].

Finally with the growing availability of 3D reconstructed VBs, we are at the threshold of bringing all these technological advances together to further improve on the accuracy and safety of diagnosing ever more subtle peripheral lesions. Asano demonstrates the fidelity VB has to the actual bronchoscopic view down to the eleventh generation airway in a case report combining VB navigation and real-time CT to guide a 2.8 mm ultrathin bronchoscope to sample peripheral nodules less than 2 cm in diameter [24]. Shinagawa also combined VB navigation with real-time CT-guided biopsy of a different lesion under 2 cm. A diagnostic yield of 65.4% was achieved, with no significant loss of yield for lesions less than 1 cm (60%) versus those greater than 1 cm (67%). Malignant, atypical adenomatous hyperplasia and benign lesions including sarcoid and non-tuberculous mycobacterium were diagnosed. In 10% of cases, absence of connecting airways to the lesion on VB redirected biopsies toward a more definitive surgical approach, and the positive bronchoscopic biopsies provided a tissue diagnosis in severely compromised elderly patients. Either way the combined approach minimized non-diagnostic or high-risk invasive procedures [116].

The advances in 2D multiplanar and 3D VR and VB imaging are making possible the accurate sampling of small and subtle peripheral lung lesions. The current ultrathin bronchoscope's limitations include the miniscule operating channel (0.8–1.2 mm) and the overly floppy bronchoscope tip. Prototypes being tested include a 4.0-mm outer diameter thin-bronchoscope with a 2.0 mm channel that can accommodate most normal sized biopsy forceps and even trans-bronchial needle for aspiration (TBNA). Reliable minimally invasive bronchoscopic sampling of these lesions will become increasingly desirable as "screening" CT scans are detecting many more and smaller non-calcified nodules (NCN) and areas of ground-glass opacities (GGO) are detected [117–119]. The frequencies of these findings range from 10 to 51%, with the overall incidence of cancers between 1.5 and 3.4%. There is reasonable hesitation to subject the majority of patients to open surgical biopsies [117–119].

Two other developments may compete with and/or complement the use of advanced 2D multiplanar imaging and 3D VR and VB in the diagnosis of peripheral lesions. EBUS probes for the lung periphery help to characterize the parenchyma prior to biopsy [120,121]. Position sensors built into the tip of bronchoscopes and sensed by skin fiducial markers or CT position marker can provide real-time guide to the bronchoscope's position relative to the target lesion [122]. Coupled with 3D reconstruction of a pre-procedural CT displayed during the procedure, there can henceforth be multiple feedback systems to very accurately guide the sampling instruments toward ever smaller and peripheral targets [123,124].

Nodal sampling

Transbronchial needle aspiration sampling of regional hilar and mediastinal lymph nodes in the diagnosis and staging of lung cancer and in the diagnosis of benign conditions have published yields of 60–90% [125]. These diagnostic sensitivities are not always achieved because of lack of uniform training in TBNA [126–128]. An approach to improve in TBNA performance is to incorporate CT guidance into the TBNA process to confirm placement of the needle tip within lymph nodes of interest. Rong *et al.* [101] in 1988 presented the initial report of improving their diagnostic yield of TBNA of mediastinal nodes from 20 to 60% with the addition of CT scan directed biopsies. Follow-up studies included patients who have had prior unsuccessful bronchoscopies with TBNA attempts or anticipated low yield due to nodal size or location. The addition of real-time CT-fluoroscopy resulted in retrieval of nodal material in 83–87.5% with rare (3%) incidence of a false negative sample [25,30]. Furthermore, the use of CT to check on needle position after a "blind" pass confirms the frequent misdirection of the TBNA needle tip in 41% of such passes, especially when lymph nodes are small [26].

The advent of VB raised the possibility to further direct more accurately TBNA by rendering the airway walls semi-transparent and hence directing the path of the aspiration needle [42,129]. In a simulated exercise involving VB and a preselected set of 35 regional lymphadenopathies, bronchoscopists marking the position along the simulated airways for TBNA insertion can have theoretical

improvement in yield if the lymph node locations can be highlighted on the VB fly-throughs. This nodal highlighting is most useful for hilar, pre-tracheals and high pre-tracheal lymph nodes; there is a trend toward, but not statistically significant, improvement for aorto-pulmonary and subcarinal stations and for smaller lymph nodes as well [130].

We recommend the availability of bedside cytopathology to further increase the diagnostic yield of TBNA and/or other diagnostic procedures by confirming the adequacy of samples retrieved under CT-fluoroscopy or VB guidance [131–133].

Endobronchial ultrasound has also been studied as an effective adjunctive method to accurately locate and direct TBNA of regional lymph nodes [134]. EBUS has the advantage of being able to also reveal in great detail presence of submucosal tumor invasion. Conversely the equipment for EBUS is expensive and the training to achieve competency quite long. To date, there have not been any controlled studies to compare the actual effectiveness of VB versus EBUS guided TBNA.

Congenital conditions and pediatric 3D imaging

Congenital airway anomalies can be difficult to discern even on 2Dmultiplanar imaging, and endoscopic evaluation especially in pediatric patients with very small airways may be limited and carry extra risk. 3D CT is preferred to assess the subtle angulation changes of some aberrant bronchi or branching patterns such as a bridging bronchus [75] (Figures 4.21 and 4.22), as well as congenital vascular rings and slings as they relate to the airway [135–138] (Figures 4.23 and 4.24). Other abnormalities documented in 3D studies to date include tracheostenosis, tracheomalacia due to esophageal atresia, idiopathic tracheal indentation, aplastic and hypoplastic main bronchus, aberrant tracheal–bronchial airway branching, tracheobronchomegally (Mounier–Kuhn disease), tracheopathia osteoplastica and acquired conditions such as tracheal papillomatosis and aspirated foreign bodies [34,35,41,71,75,139–143]. Although the availability of MPR combined with 2D planar axial CT already results in a very satisfactory 89.5% agreement with the actual bronchoscopic findings, the addition of VB brought the accuracy of prediction up to 100% in one study with diverse disorders [41]. Congenital tracheoesophageal fistulae of various types mapped with 3D CT can aid surgical resection and reconstruction (Figure 4.25). In pediatric imaging, specific attention must be given to radiation dose techniques customized to the size of body [19,140,144]. Low-dose spiral CT using a lower tube current at 50 mAmp does not appear to degrade image quality of 3D surface rendered images when compared to conventional current of 240 mAmp and this would represent another method of radiation sparing for the patient [145]. Using multi-slice technology with rapid acquisition times may spare children the additional risks and costs of sedation and anesthesia [146].

Future applications

Improved accuracy in radiologic guidance to reach peripheral lesions is currently used primarily to improve bronchoscopists' diagnostic yield. A number of thoracic malignancies diagnosed may however be unresectable because of local extension of disease or poor functional status of the patient. Repeatable accurate localization of such lesions may allow us to expand local therapy to otherwise unapproachable peripheral lesions. Types of therapy may include brachytherapy via afterloading catheters, development of airway delivered radio-frequency ablation catheters and directintratumoral injection or infusion of cytotoxic or biologic response modifiers.

Further refinement of functional airway imaging with density measurement of air-trapping or hyperpolarized noble gas imaging may be combined with 3D VR and VB airway guidance to direct surgical or bronchoscopic LVRS.

Currently available virtual reality bronchoscopy simulators using a set of preloaded VB programs have been found useful in the training of new fellows [52]. Further refinement and rapid generation of specific clinical cases using VB may allow a realistic "run-through" of particularly challenging or potentially high-risk cases.

Conclusion

Airway imaging extending from central airways to the distal segments is currently undergoing

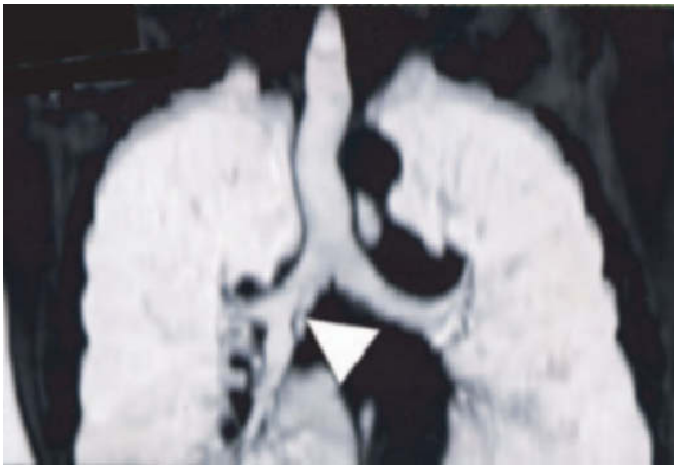

Figure 4.21 Accessory bronchus. An accessory blind ending bronchus arises from the medial aspect of the right lower lobe bronchus (arrowhead), VR CT.

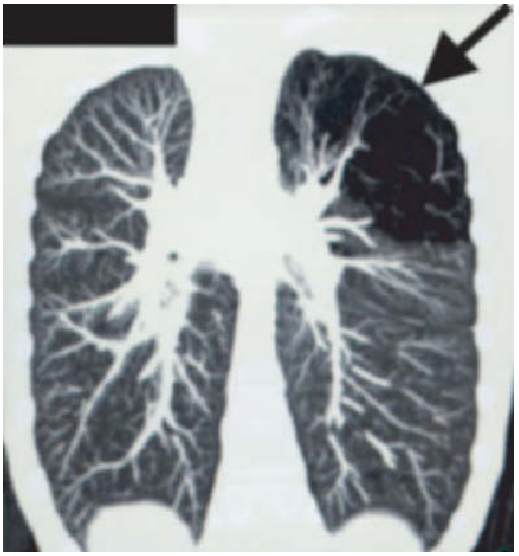

Figure 4.22 Bronchial atresia. Hyperinflated and hyperlucent left upper lung is observed in this patient with bronchial atresia (arrow), VR MDCT.

another revolution led by MDCT and 3D VR tools. The combined application of the latest advances in MDCT and 3D VR will allow generation of high-quality, real-time multidimensional tracheobronchial images, including "virtual bronchoscopies" (VB). The near future will bring a greater refinement of these tools including an exploration of functional imaging of the lungs using both CT and MRI with hyperpolarized gases. Beyond vastly expanding the diagnostic power of current airway CT, properly designed protocols can create high-resolution lung parenchyma imaging (HRCT), CT angiography or 3D airway studies from a single examination. Structures such as central airways, secondary pulmonary lobules and their pathology can also be studied in their entirety and findings may be described in a fashion that more closely resembles that encountered by the bronchoscopist or surgeon.

Tissue acquisition remains paramount in the firm diagnosis of pulmonary pathology as neither improved anatomic nor metabolic characterization of lung lesions suffice to warrant start of cytotoxic chemotherapy or radiotherapy for suspected cancers. The role of empiric therapies for inflammatory or infectious conditions is more open to discussion, but the improved guidance and sampling techniques argue for aiming toward a higher percentage of pathology confirmed cases before initiating therapy.

Limitations remain in this rapidly evolving field as artifacts continue to interfere with the volume rendered 3D images of the airway and lung parenchyma. Retained secretions may give a false impression of mucosal lesions and the complex folds of the airway mucosa, especially after thoracic surgery with lung resections and airway anastomosis, remain difficult to interpret. Respiratory and cardiac motion artifacts may be difficult to completely

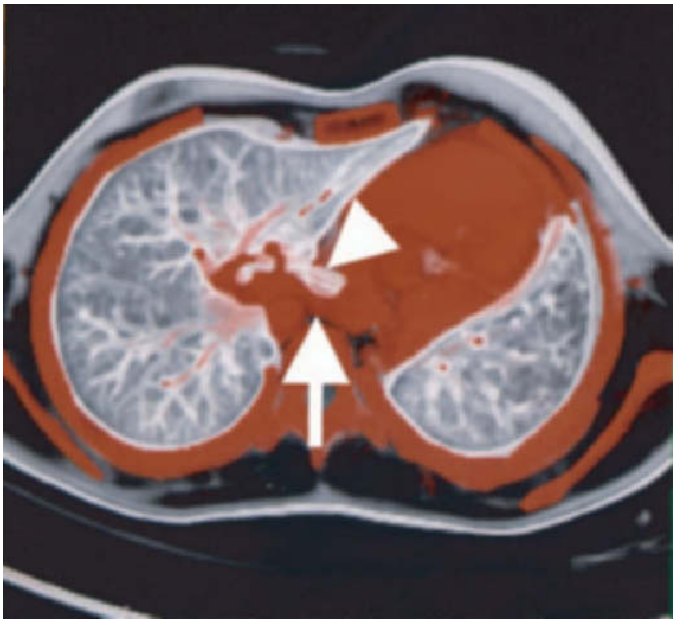

Figure 4.23 Pulmonary sling. A superior perspective VR MDCT with CTA demonstrates the left pulmonary artery (arrow) extending behind the bowed trachea (arrowhead).

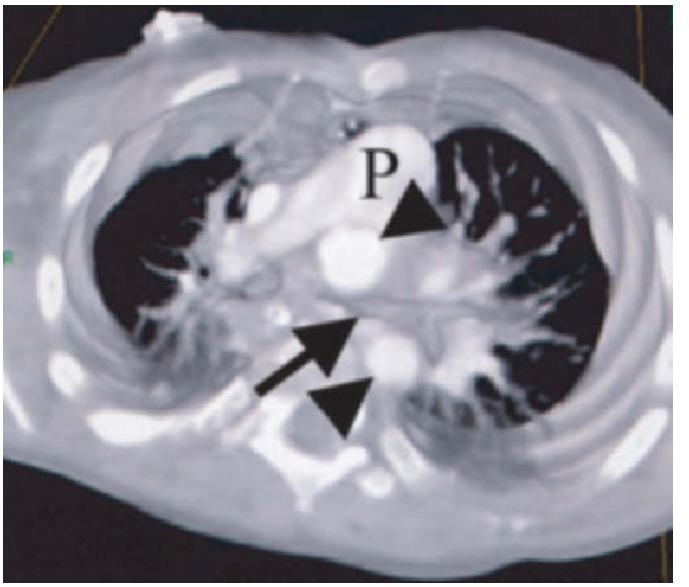

Figure 4.24 Transposition of the great arteries. A narrowed aortic arch (arrowheads) is associated with bronchomalacia of the left lower lobe bronchus (arrow) on this VR MDCT image. Pulmonary artery (P).

eliminate. Subtle surface changes including hues and textures are at present not well represented. 2D imaging therefore will remain for a time the cornerstone of airway imaging and the use of 3D must be goal defined and is likely to be in the arena of improving diagnostic confidence and more sophisticated interpretation of the acquired dataset than in early lesion detection.

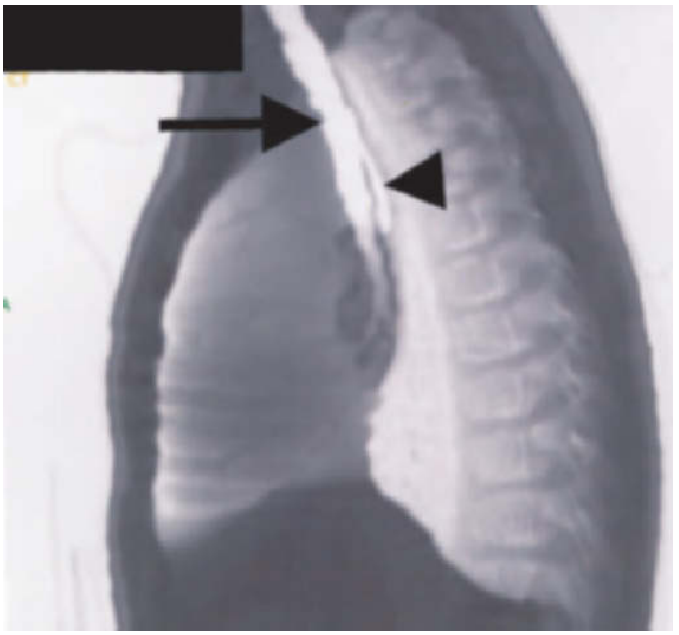

Figure 4.25 Tracheoesophageal fistula. A pouch (arrowhead) arising from trachea (arrow) remains in this patient after tracheoesophageal fistula repair. Lateral view VR MDCT.

Available computational speed and innovative software have made MDCT and 3D VR and VB realistic and practical tools for patient care. There is a move from hard copy display (film) to soft copy workstations and archiving systems to handle the 600–800 slices that may be routinely produced. Consolidation of the multiple imaging approaches and development of a network within a single institution and even for remote locations will foster closer multimodality and multispecialty interaction with the attainable goal of a seemless imaging clinical environment within sight. The future holds potential for greater growth and networking of imaging to hospital sites including the bronchoscopy suite, operating theater and clinic.

The complimentary role of radiologic imaging to the diagnosis and management of chest diseases is well recognized. It is now more than ever important to integrate the ongoing CT advances into our practice of diagnostic and interventional bronchoscopy. Its maximal impact is defined not only by its solo imaging capabilities but also in its synergistic role to positively affect outcomes in diagnosis and management of a myriad of lung diseases.

Glossary

Conventional/Incremental CT—Step-wise, interrupted patient/table translation and gantry rotation so that the photons prescribe a slice.

Gantry—The circle through which the patient moves during scanning and which contains a rotating radiation source and detectors (one rotation ~0.4–0.5 s).

Helical/spiral CT (HCT/SCT)—Continuous patient translation and gantry rotation so the photons prescribe a helix.

Interpolation—A continuous function is constructed from discrete sample points. Slices are made from a helix of raw data.

Maximum intensity projection (MIP)—Only density values above an assigned threshold are displayed.

Minimum intensity projection (MinIP)—Only density values below an assigned threshold are displayed.

Multidetector row helical CT (MDCT)—Multiple detectors (e.g. 4–16) activated during a single gantry rotation.

Multiplanar reconstruction (MPR)—Pixels are reordered into alternate, nonaxial, straight imaging plane.
Curved multiplanar reconstruction (CMPR)—Pixels are reordered into an alternate nonaxial imaging display that is one pixel thick but usually curved to a structure of interest.
Pixel—Picture elements that make up a CT slice (i.e. 512 × 512).
Segmentation—Selection and display of voxel elements to display a structure of interest. Identify and display values representing structures of interest by determining (usually based on intensity) whether a voxel element is part of or not part of the structure of interest.
Shaded surface display (SSD) Surface rendering—A surface is determined from the volume data. It is described with the projection of polygons.
Slab editing—Rather than performing reconstruction on a single slice, the entire volume of a slab of several contiguous planar images stacked together to create a certain intermediate thickness is used.
Staircasing/stairstepping—A 3D artifact that occurs when the distance between slices is much greater than the pixel size.
Thresholding—Voxels are determined to belong or not belong to a preselected range of density values (either absolute or a range).
Volume rendering—Directly renders volume data. Can create translucent and opaque, surface-type images based on density values available.
Voxel—Volume element to construct a volume dataset from contiguous slices.
Isotropic voxels—Voxels with similar dimensions in all threeplanes and in which the spatial resolution in any plane approximates that in the axial plane.
x–y plane—The axial plane displayed on a CT slice.
z-axis—The axis of the patient from head to toe. Slice thickness measured in z-axis.

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5

CHAPTER 5

Medical simulation: current uses and future applications

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Introduction

The evolution of computer technologies during the past half-century has fostered broad and dramatic changes in communications, industry, and education. And while the human body itself has not changed appreciably during this period, advances in computing, particularly in training, have undoubtedly influenced the field of medicine. Computer-based simulation is well suited to medical training, and recent technological advances have enabled the field to expand significantly [1–3].

This chapter outlines the current status and anticipated future trends for simulation in medical training with an emphasis on thoracic procedures. Definitions of "simulation" vary. In the medical training arena simulation has been defined to include such low-tech examples as the use of hollowed cantaloupes connected in series to simulate colonic anatomy for endoscopy training [4], and even the use of animals as a simulation of the human patient [5]. In this chapter we use the term simulation to mean computer-based devices that simulate reality for the purpose of acquiring, maintaining and/or assessing medical knowledge and skills.

Parallels with aviation

Medical training has many parallels with aviation training, which provided the impetus for the first computer-based training simulators. Like performing surgery, flying an aircraft demands precision in psychomotor skills, with the safety and well-being of large numbers of people entrusted to these skills on a daily basis. Today, practically all commercial pilots are trained and certified using flight simulators. The four factors that probably account more than any others for the aviation industry's embracing of simulation are the same four factors that have made simulation so well suited to medical training:

1 Simulators are safe. It is possible to train emergency and hazardous procedures with no risks to dependents (passengers in aviation; patients in medicine).

2 Simulators are flexible. With the amount of computational power available in modern simulation systems, it is possible to provide users with a wide variety of patient scenarios in a relatively short period of time, including emergencies rarely encountered but for which trainees must be prepared.

3 Simulators can provide objective feedback to trainees on a multitude of performance metrics, allowing tracking of user progress and assessment of specific skills.

4 Simulators are cost-effective. Particularly when one considers the number of potential training scenarios that can be used, computer-based simulation provides a great deal of training for the investment. When simulators are used for aviation training, aircraft do not have to be taken out of primary service to accommodate training needs; medical simulators similarly reduce the amount of time needed for clinical training in the operating

room, the endoscopy suite or other facilities whose primary function is patient treatment. Simulators can also obviate the need for animals and human cadavers, whose costs are cumulative. Insurance companies have provided insurance premium discounts to both pilots and their employers trained and certified on flight simulators. This milestone was recently achieved for medical simulators when a Boston-area insurance firm began providing malpractice insurance discounts to providers trained on simulators.

Aviation simulation has surpassed a critical point when its value (both functional and economic) in aviation training is universally recognized, and its future assured for as long as humans wish to fly. This is significant to medical simulation, for it presages a similar outcome as exposure to the technology and its acceptance grow in the medical sector.

Simulation's recent history

Medical simulation is a young field. The first efforts to develop computer interfaced simulators for medical instruction occurred in the 1960s, and the first commercialized device did not appear until the early 1990s. At this time, the processing burden required of real-time computer-generated displays made virtual reality simulation cost-prohibitive as a commercial venture. But steady progress in computer chip technology has recently brought the cost of medical simulators down to within the budgets of most medical teaching institutions.

Computer-based medical training simulators fall under two broad categories: (a) computer-controlled mannequins (CCMs) and (b) virtual reality simulators. These two categories can crudely be distinguished by their emphasizing the external patient and the internal patient, respectively, though there is much overlap in their functions and capabilities.

Computer-controlled mannequins

The first medical procedure simulator was completed at the University of Southern California (USC) with the Sierra Engineering Company in the late 1960s [6,7]. Sim One was designed for training in anesthesia, and featured a heartbeat, carotid pulses, blood pressure, open and closed mouth, blinking eyes, muscle fasciculation and the ability to cough. The device could also respond to several intravenous drugs, and reacted appropriately to such gases as oxygen and nitrous oxide. Despite these capabilities, and the fact that the simulator was used for several years at USC, the project was terminated about 1975, generally due to lack of broader interest and funding [8]. It was not until the late 1980s that realistic anesthesia simulators began to reappear. The Comprehensive Anesthesia Simulation Environment (CASE) [9] at Stanford and the Gainesville Anesthesia Simulator (GAS) [10] became commercially available in the early 1990s. CAE-Link Corporation sold the CASE simulator (later called the Eagle Patient Simulator) and Medical Education Technologies, Incorporated (METI) sold GAS as the Human Patient Simulator.

Virtual reality simulators

Among the first attempts to develop virtual reality simulators were those described in 1989 and 1990 for training in upper and lower gastrointestinal endoscopy [11,12]. A series of papers published in 1992 as a supplement in the journal *Endoscopy* provides an overview of the state of the art at this relatively early stage [13–18]. At that juncture, prognoses for the future potential of simulation to revolutionize endoscopy training ranged from enthusiastic [16] to skeptical [18].

It wasn't until the mid-to-late 1990s, when computer processing technology had evolved to the point that real-time simulation of medical procedures was feasible on a PC, that production of commercial simulators began. In April 1998, the CathSim Vascular Access Training Simulator (Immersion Medical, formerly HT Medical Systems, Gaithersburg, Maryland) was released [19]. CathSim, a stand-alone simulator for training in IV insertion, was developed in collaboration with the Department of Nursing, Food and Nutrition at Plattsburgh State University of New York [20]. This simulator integrated 3D graphics, multimedia and force feedback, allowing the user to feel the characteristic "pop" of the needle through the skin and into the vein of the virtual patient.

Since that time, several other virtual reality simulators have been developed. Due to limitations in current computing and haptic (simulation of touch) technology, the focus has been limited primarily to minimally invasive procedures such as endoscopy [21–26], catheterization [27,28] and laparoscopy [29,30]. However, rapid advances in computing technology give hope that full open surgical simulation is not far off.

Advantages of simulation

Problems with the current medical training paradigm are widely acknowledged. In their oft-cited 1999 report, the Institute of Medicine identified inadequate education and training of clinicians as a key problem with quality of healthcare in the United States, with between 44 000 and 98 000 human deaths being attributed yearly to medical error, adding an estimated $29 billion to the annual cost of healthcare [31]. There is a growing cadre of medical educators who recognize the potential of simulation to help ameliorate this problem through improved training and subsequent patient safety. This conviction is based in part on the wide range of advantages that simulation provides, including:

- no risk to patients – trainees err on a simulator, not a patient
- no risk to trainees (e.g. from exposure to patient blood-borne pathogens)
- opportunity to gain procedural familiarity and comfort through unlimited repetition
- providing a full range of patient cases including complications, pathologies and anatomical variants rarely encountered but for which practitioners must be prepared
- objective measurement of specific skills and procedural competence through case-based and longitudinal data tracking of trainee performance
- standardized training, ensuring all trainees are exposed to a standard set of patients
- introducing new procedures to practicing physicians, speeding their adoption
- freedom from ethical controversy (no patient consent required; no use of animals)
- anatomical and physiological realism – animal anatomy differs from human anatomy; cadaver tissues handle and respond differently to living tissue
- viewing the "patient" in ways impossible during actual procedures (e.g. transparency views allowing for visualization of thoracic structures such as lymph nodes, the great vessels and heart during a simulated bronchoscopy)
- stand-alone training not requiring the constant presence of an instructor
- selection of content to focus on areas of greatest need for improvement
- facilitating learner self-monitoring, and assessment by instructors
- potential to dramatically lower costs through improved clinical outcomes.

Simulators for bronchoscopy and other thoracic procedures

Virtual reality bronchoscopy simulator

The only commercially available virtual reality simulator for bronchoscopy is the AccuTouch® Endoscopy Simulator (Immersion Medical) (Figure 5.1). Originally introduced in 1999 as the PreOp Endoscopy Simulator [21], this device consists of a proxy flexible bronchoscope, a robotic interface device, a standard PC with monitor and simulation software.

The user inserts the proxy flexible bronchoscope through one of the "patient's" nares and into the robotic interface device. This interface device tracks the motions of the bronchoscope and provides force feedback, allowing the user to feel realistic tactile sensations, such as the wedging of the scope in a distal bronchus. The proxy bronchoscope looks, feels and behaves like an actual bronchoscope. Electromechanical devices within the bronchoscope track manipulations of the tip control lever, the suction button and video buttons. The working channel is instrumented to track and provide force feedback to tools, such as biopsy forceps and transbronchial needle aspiration (TBNA) needles.

The monitor displays computer-generated images of the airway as the user navigates through the virtual anatomy in real-time (Figure 5.2). High-resolution computed tomography (CT) data sets, or other data sources such as the National Library of Medicine's Visible Human Project [32], are used

to generate the 3D anatomy. This allows development of a wide variety of cases, reflecting the full range of human anatomy and pathology. Mucosa is given a realistic look by adding texture maps to the geometry. The texture maps are based on actual bronchoscopic images.

Figure 5.1 AccuTouch Endoscopy Simulator for Bronchoscopy. Reproduced with permission from Immersion Corporation, Copyright © 2006 Immersion Medical Corporation. All rights reserved.

Not only are the virtual patients anatomically correct, but they also breathe, cough, bleed, exhibit changes in vital signs and respond audibly to discomfort or pain. Touching the walls of the virtual airway elicits a cough and provides the appearance of mucus on the scope tip. The mucus can then be washed off or suctioned away. Complications can arise, such as lidocaine toxicity, causing a cardiac arrhythmia and/or seizure.

At any point during the simulation, the user may activate one or more of the augmented reality features designed to enhance the learning experience. An "External View" (Figure 5.3) provides a view of the virtual patient's entire bronchial tree, including bronchoscope location, that can be rotated, zoomed and panned. Users can interactively learn the bronchial anatomy by using "Road Signs," which provide abbreviations of the bronchial tree segments visible in the endoscopic view (Figure 5.4). A "Transparency View" (Figure 5.5) can be accessed to see and learn important anatomic structures adjacent to the tracheobronchial tree, such as the great vessels, trachea and heart. This is especially helpful in learning TBNA, which involves blindly sampling lymph nodes in the mediastinum. In addition, a "Virtual Attending" can be activated to provide hints and suggestions as the virtual examination proceeds.

The software tracks a variety of metrics, and presents users with a report at the end of each examination. Examples of metrics include time

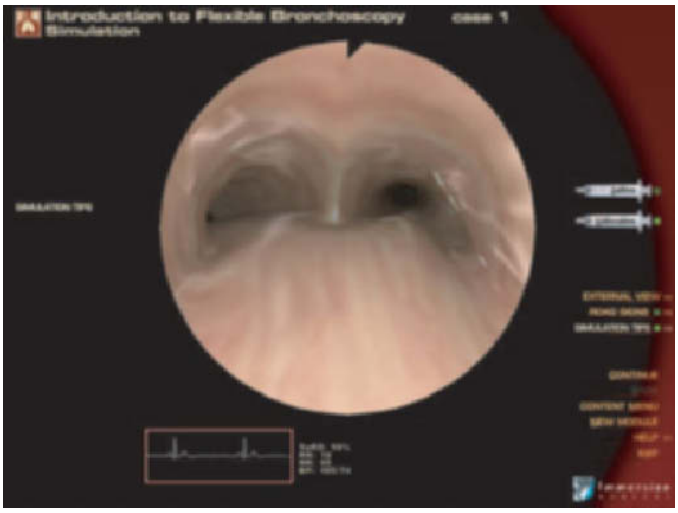

Figure 5.2 Endoscopic view of virtual airway. Reproduced with permission from Immersion Corporation, Copyright © 2006 Immersion Medical Corporation. All rights reserved.

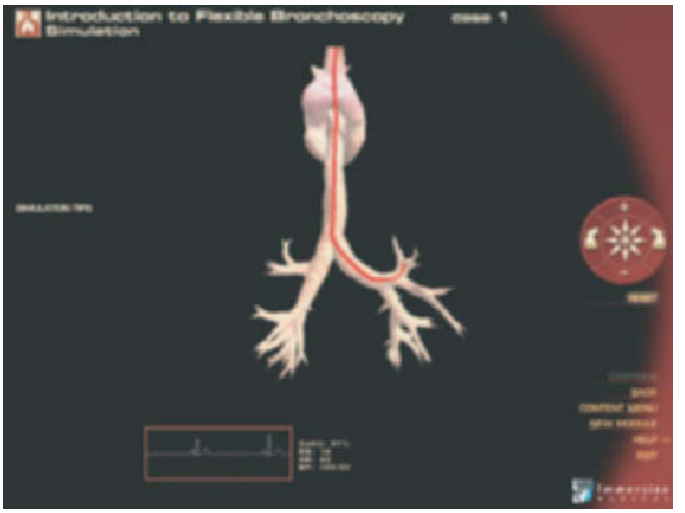

Figure 5.3 External view of tracheobronchial tree. Reproduced with permission from Immersion Corporation, Copyright © 2006 Immersion Medical Corporation. All rights reserved.

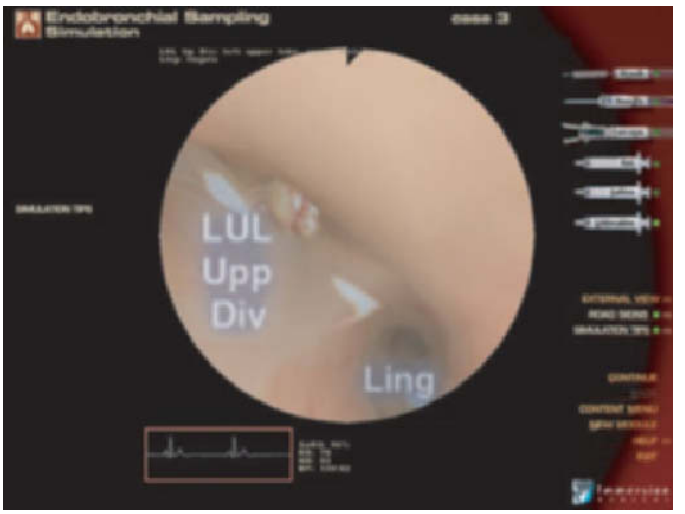

Figure 5.4 Simulator road signs. Reproduced with permission from Immersion Corporation, Copyright © 2006 Immersion Medical Corporation. All rights reserved.

of procedure, percentage of bronchial segments viewed, amount of lidocaine used, number of scope collisions with airway walls and order of bronchi visualized. This allows for the tracking of a user's progress over time and for comparisons with other trainees.

Computer-controlled mannequins

Computer-controlled mannequins typically consist of a life-sized human mannequin animated with a variety of electromechanical or pneumatic devices producing respiratory movement, palpable pulses, heart and lung sounds, realistic airway anatomy, twitches and spasms and simulated body fluids (e.g. blood and urine). A system computer governs interactive mathematical models of drug function, metabolism, cardiac function, gas exchange and fluid balance. CCMs simulate many clinical scenarios, and may provide vital signs, breath and heart sounds, arterial pulses, pupilary reactions to light and trauma, lungs that take in oxygen and exhale carbon dioxide and a tongue that swells. The computer allows the educator to create complex scenarios that present various challenges to the learner [33]. Users can learn how to recognize and treat reactions to an extensive library of drugs, and

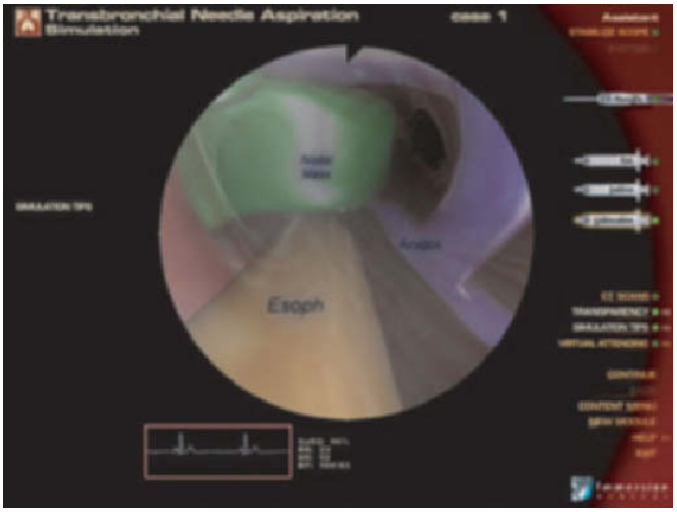

Figure 5.5 Transparency view for transbronchial needle aspiration (TBNA). Reproduced with permission from Immersion Corporation, Copyright © 2006 Immersion Medical Corporation. All rights reserved.

to perform anesthesia, intubation, chest tube insertion, needle decompression, pericardiocentesis and other interventions [34]. CCMs are highly suitable for team training in patient management and emergency response skills in a suite that recreates the patient care environment.

The most common commercially available CCMs are the Human Patient Simulator (HPS™) (METI, Sarasota, Florida) and SimMan™ (Laerdal, Stavanger, Norway) (Figures 5.6 and 5.7). Thoracic and airway procedures that can be performed on CCMs include endotracheal intubation, cricothryroidotomy, chest tube insertion and needle thoracotomy. Another thoracic simulator that is not yet commercially available is the VIRGIL® Chest Trauma Training Simulator System developed in Boston at CIMIT® (Center for Integration of Medicine & Innovative Technology), a nonprofit consortium of academic and research institutions.

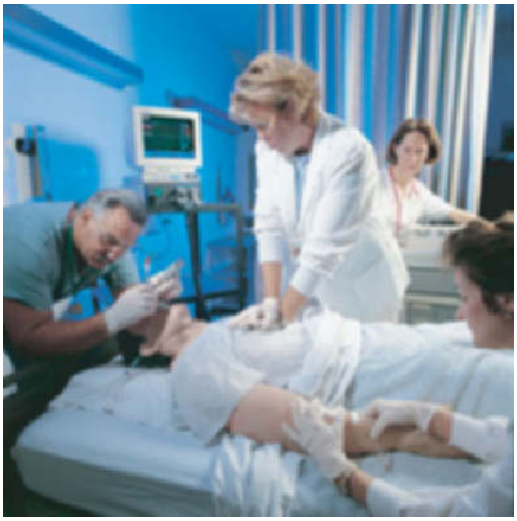

Figure 5.6 Human Patient Simulator. (Reproduced with permission from Medical Education Technologies, Incorporated.)

Other thoracic simulators

Trauma Man™ (Simulab Corporation, Seattle Washington) (Figure 5.8) is a mannequin that can simulate a variety of trauma procedures including chest tube insertion and pericardiocentesis. While Trauma Man is not computer controlled it is significant because it was the first simulator to be approved for Advanced Trauma Life Support (ATLS) training and certification by the American College of Surgeons Committee on Trauma [35]. This simulator includes a layer of simulated skin, a layer of simulated tissue to mimic the intercostal muscles and parietal pleura, ribs, airflow inside the pleura for a realistic response during a procedure and inflatable lungs to simulate breathing. The heart and pericardium can be filled with simulated bodily fluids.

Figure 5.7 SimMan. (Reproduced with permission from Laerdal Medical Corporation.)

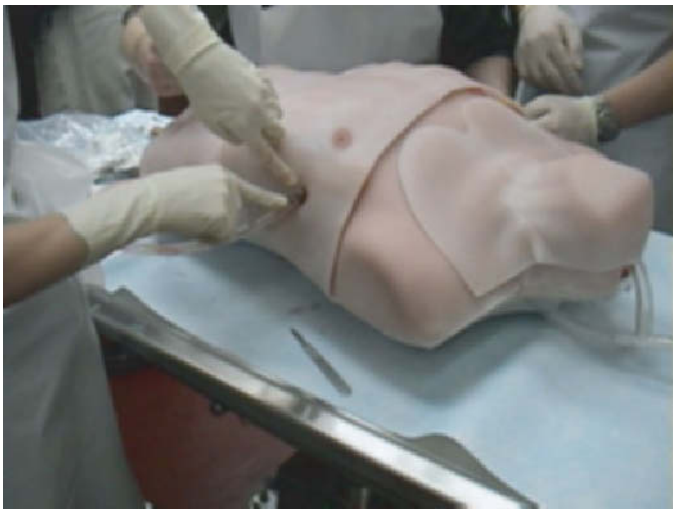

Figure 5.8 Trauma Man. (Reproduced with permission from Simulab Corporation.)

Validation studies

Due mainly to their relatively recent appearance, there are only a modest number of studies to date evaluating the performance and efficacy of commercialized simulators. The most studied is the AccuTouch bronchoscopy simulator [36–42]. Here we present further detail on three published full-scale studies that demonstrate both content validity (capacity to enhance intended performance skills) and construct validity (ability to discriminate users based on their level of experience) on this device.

Rowe *et al.*, 2002

This study involved 20 pediatric residents with no prior experience with flexible bronchoscopy (FB). The simulator group ($n = 12$) performed one bronchoscopic intubation on a child, then trained on the simulator (average 17 virtual patient cases, and 39 min), then performed a second live procedure. The control group ($n = 8$) also performed two live procedures, but with no intervening training. All live procedures in this study were videotaped and later reviewed and scored by anesthesia attending physicians who were blinded to subject identity and group.

Simulator group residents improved significantly in all recorded measures: time to completion from nasal entry to visualization of the carina (5.15 to 0.88 min, $p < 0.001$), number of collisions between scope tip and mucosa (21.4 to 3.0, $p < 0.001$), amount of time viewing the mucosa (2.24 to 0.19 min, $p < 0.001$) and the amount of time viewing

the airway (58.5 to 80.4%, $p = 0.004$). Simulator group residents also scored significantly higher for all measures than did the control group residents in the second procedure: time to completion (0.88 versus 5.95 min, $p < 0.001$), number of collisions (3.0 versus 21.38, $p < 0.001$), time viewing mucosa (0.19 versus 2.73 min, $p < 0.001$) and time viewing airway (80.4 versus 60.3%, $p = 0.03$). There were no significant differences among the following procedure groupings: initial procedure for the experimental group, initial procedure for the control group and second procedure for the control group.

In summary, the bronchoscopy simulator demonstrated significant advancement in fiberoptic intubation skills.

Ost *et al.*, 2001

This multicenter study aimed to determine: (a) whether the simulator could differentiate expert from novice bronchoscopists, and (b) whether use of the simulator would improve the rate of bronchoscopy skill acquisition for new pulmonary fellows. The three study cohorts were as follow:

1 *Experts* ($n = 9$) had performed at least 500 prior bronchoscopies

2 *Intermediates* ($n = 8$) had performed between 25 and 500 bronchoscopies

3 *Novices* ($n = 11$) had performed no bronchoscopies.

Each participant performed two virtual patient cases on the simulator, which recorded performance measures. The performance records of the novices were also used to compare their learning curve with that of new fellows trained using conventional methods.

Experts outperformed intermediates on the simulator, who in turn outperformed novices in terms of procedure time, percentage of segments visualized, time in red-out and wall collisions. New fellows demonstrated significantly improved skill in terms of these same variables after performing 20 bronchoscopic simulations. These fellows also performed better than the conventionally trained fellows during their first real bronchoscopies as assessed by procedure time (13:35 versus 19:28 min, $p = 0.001$), a bronchoscopy nurse's subjective quality assessment score (7.7 ± 0.3 versus 3.7 ± 2.5, $p = 0.05$) and by quantitative bronchoscopy quality score (percentage of segments correctly identified/procedure time, 0.119 ± 0.015 versus 0.046 ± 0.034, $p = 0.03$).

In summary, the bronchoscopy simulator successfully discriminated practitioner experience level, and accelerated the acquisition of bronchoscopy expertise relative to conventional training methods.

Colt *et al.*, 2001

This study involved two cohorts: (a) five novice pulmonary and critical care medicine fellows in the early stages of their first year of training, and (b) four third-year fellows, each of whom had performed more than 200 FB procedures. The novices received an 8-h teaching curriculum, as follows:

- 1-h observation of an online video about FB,
- 1-h instructor-led overview of tracheobronchial anatomy and FB inspection techniques,
- 2-h supervised group instruction on the simulator, and
- 4-h unsupervised individual practice using the simulator.

Novices were given a pretraining performance test that entailed performing a FB inspection of normal laryngotracheobronchial anatomy on the simulator. Following the 8-h training course, the novices were once again tested on the simulator, using a novel virtual patient case. Testing of the experienced fellows was identical to the novice group's post-training test, except that each fellow first had a 30-m session of supervised practice using the simulator.

Outcome measures were generated by the simulator, and defined as follow:

- *dexterity* = number of mucosal contacts per minute
- *accuracy* = thoroughness as measured by number of bronchial segments missed
- *speed* = procedure duration from start to finish
- *time in red-out* = percentage of time that scope tip was against mucosal wall.

Novices showed statistically significant improvement between pre- and post-training tests for both dexterity (13.8 to 11.4, $p = 0.022$) and accuracy (4.4 to 0.8, $p = 0.029$). There were no statistically significant differences between novice scores on the post-training test and the scores of the experienced physicians for the following measures: speed (10:16

versus 7:01 min:s), dexterity (11.4 versus 9.8) and time in red-out (26 versus 24%).

The study authors concluded that "a short focused course of instruction and unsupervised practice using a virtual bronchoscopy simulator enabled novice trainees to attain a level of manual and technical skill at performing diagnostic bronchoscopic inspection to those of colleagues with several years of experience."

While larger scale studies are necessary for widespread adoption of simulation for training and credentialing, the fact that the studies mentioned earlier reported statistically significant findings despite their small sample sizes illustrates the potential of simulation-based training and assessment. Not only is there strong evidence for the efficacy of the bronchoscopy simulator, but also for other virtual reality simulators for procedures such as gastrointestinal (GI) endoscopy [43–48], laparoscopy [29,30], peripheral IV insertion [49] and catheter-based cardiovascular procedures [28].

Looking ahead

For a number of reasons, interest in and demand for simulation is expected to grow substantially in the coming decades. Immediately attainable benefits include meeting growing training needs for existing and new minimally invasive procedures, and incorporating the assessment of manual dexterity and motor skills into the credentialing process. Future potential applications of simulation technology include the ability to conduct preprocedural rehearsals on specific patients, and performing pre-mapped robotic surgery. We briefly discuss each of these here.

The use of simulation to meet the training needs for new and existing minimally invasive procedures is already happening. Virtual reality simulators and CCM simulators are now installed at medical facilities around the world. Skills for performing procedures ranging from GI and pulmonary endoscopies to endovascular and trauma interventions can now be acquired, maintained and evaluated with simulators, albeit at a yet relatively small fraction of training facilities. The development of new minimally invasive procedures, and instruments to perform them, should stimulate a further need for simulators to train in them. Thoracoscopy and video-assisted thoracic surgery (VATS) techniques are becoming increasingly more common, and simulators can provide the opportunity to develop these skills without risk to patients. With FDA approval in 1999 of two stent graft devices for endovascular abdominal aortic aneurysm (AAA) repair, this procedure is increasingly being offered as a first choice over conventional surgery. Yet, despite certain advantages over conventional AAA repair, complication rates remain high and the clinical status of AAA stent grafting remains uncertain a decade after its first being performed on a human patient [50,51]. It is likely that these problems are largely iatrogenic, and we believe that simulation-based training and rehearsal could do much to alleviate them.

Simulators could greatly strengthen the physician certification process by allowing licensing boards and hospital credentialing committees to gather objective data on physicians' ability to perform specific procedures. Motor skills and manual dexterity are not tested during the Board Certification process. But just as one would not want their pilot to be certified to fly by taking a written or oral exam without demonstrating the ability to perform in a cockpit, it is in the interest of patients' safety that physicians demonstrate practical competency in a procedure before performing it in the clinical setting. As data accumulate supporting the effectiveness of simulators, it seems likely that their adoption into the certification process will follow [52].

Another likely future application of simulation to medicine is preoperative rehearsal. Patient-specific data derived from magnetic resonance imaging (MRI) and CT scans would be downloaded to a simulator and the physician could then rehearse the planned intervention. This would be particularly useful for complex cases that present a variety of challenges. Those challenges could be encountered and mastered in a virtual environment before beginning the actual procedure.

The arrival of robotically assisted surgery is one of the latest applications of technology to medicine. The two leaders in this field are the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, California) and the ZEUS® Robotic Surgical System (Computer Motion, Goleta, California). The surgeon sits at a remote console and operates

hand-held devices while viewing the patient through a video monitor. Hand movements are relayed to the robot, which "performs" the procedure directly on the patient. The robot operates through smaller incisions, performs the work without tremor and minimizes surgeon fatigue with an ergonomic operating environment. These devices are large and expensive – they sell for approximately $1 million plus maintenance/equipment replacement costs – but they are gaining popularity [53].

A logical extension of robotic surgery is telesurgery, in which the distance between the physician and the patient is measured in miles, not meters. In September 2001, the first trans-Atlantic telesurgery operation was achieved when a physician working in New York performed a laparoscopic cholecystectomy on a patient in France by controlling the movements of a surgical robot (ZEUS) [54]. The operation was successful and the patient, a 68-year-old woman, was discharged two days later. Telesurgery has the potential to globalize medical procedures, allowing the delivery of the best skills and techniques to patients practically anywhere in the world.

As technological advances in medical robotics continue, might the day come that robots perform surgery with no direct human guidance? By combining the use of simulators to perform pre-surgical rehearsal on individual patient cases, with the capabilities of surgical robots, specific interventions could be "pre-performed" using the simulator, and the procedure template then played-back through the robot which would perform the actual procedure. In addition to the advantages of robotically controlled surgery mentioned earlier, removing the human presence entirely would permit much greater speed of operation, necessitating shorter anesthesia times and expediting post-surgical tissue healing. A potential drawback is the inevitable time lag between initial patient mapping and the robotic surgery; because biological systems are not static, significant anatomical and physiological changes during the interim might render the template obsolete. While the idea of a robot taking a human's life into its "hands" may sound somewhat macabre, pre-mapped robotic surgery is not a great conceptual leap from telesurgery. Meeting the primary challenges – including mapping a patient's specific condition into a simulator, then transferring the procedural template to the robot's command system – is technologically feasible.

Conclusion

Human healthcare needs and costs can be expected to rise for the foreseeable future. These trends favor less costly, more efficient and more rigorous methods of acquiring, maintaining and evaluating procedural knowledge and skill. It is now fair to say that medical simulation has moved beyond its infancy and taken a legitimate place in medical training. Early adopters are reporting positive results and this is reflected in the findings of published studies. It is reasonable to expect that all major minimally invasive surgical procedures are likely to be simulated in the years ahead. The numerous advantages of simulation over conventional methods of training and credentialing, combined with ongoing improvements in technology and the cost of obtaining it, herald a bright future for simulation's place in medicine. The question is not whether simulation is here to stay, but what horizons it may have in store.

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6

CHAPTER 6

Bronchoscopy and computer technology

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There is no reason anyone would want a computer in the home

Kenneth Olsen, quoted in Wurster, *Computers*

640 kilobyte ought to be enough for anybody

Bill Gates, quoted in Wurster, *Computers*

I never heard my grandchildren say that the speed of their computer is enough . . . Just tell your readers the prophecy that the number of transistors on a single silicone chip will be doubling every 18 to 24 months (e.g. Gordon Moore's law) will hold true for another 20 years

Craig Barrett, quoted in Wurster, *Computers*

Introduction – a short history of computer technology

> In the mid 90s in a movie on television a strange but somehow familiar noise suddenly hit my ear; it was the sound of a typewriter. By then we already had difficulties finding one for filling out forms when necessary, as computers had almost completely replaced them.
>
> Frankfurter Allgemeine zeïting

After the invention of the rigid bronchoscope by Killian in 1897 and of the fiberscope by Ikeda in 1966 probably the next revolutionary development in bronchology was the introduction of computer technology. The microchip is the most successful piece of technical equipment that mankind has ever invented. When the first transistor, a crude device of wires welded onto a metal block was constructed in December 1947 nobody could have foreseen the future and that its creators would be awarded the Nobel Prize. To understand the almost dizzying speed of development in computer technology and to make some extrapolation on what it might hold in store for the future it might be helpful to take a brief look back on its development.

In 1646, the Englishman Sir Thomas Browne first used the term "computer" referring to time calculators for the development of calendars, and well into the twentieth century, women who calculated tables for construction or astronomy were called "the computers." The term calculation is derived from Latin "calculus" (little stone) used for counting like the Abacus described by Herdodot in the fifth century BC, together with the term μεχηαναι (mechanics) describing war machines for increasing human power. The first mechanical calculators were developed by Schickard in 1623, Pascal in 1642 and Leibnizt in 1673, the latter being able to perform the four basic calculations. In 1805 Jacquard constructed the first automatic weaver's loom steered by punch cards that had been produced by Vaucanson. The device became the prototype of the "digital graphic computer" the model for the man–machine interface. Early machine language was developed by Leibntz's son in 1806. The first use of punch-card-driven computer technology was made by Hollerith during the American caucus of 1890. The calculation was very correct but the results were deliberately falsified as they were so unprecedented.

Figure 6.1 The Harvard Mark 1, built in 1944, measuring 17 m and weighing 5 tons. With 750 000 parts for reading and processing data it needed 1 s for a simple addition. Programming was performed by switching cable connections and data were provided on punch cards. "Computers in the future may weigh no more than 1.5 tons," Popular Mechanics 1949. (Quoted from Wurster C. Computers. Eine illustrierte Geschichte. Cologne: Taschen publishers 2002.)
Source: Das Fotoarchiv/SVT.

As computer technology evolved, interfaces for man–computer communication had to be developed. In Germany Konrad Zuse from 1934 to 1941 developed several models culminating in his V3 which consisted of 2200 telephone relays and a program on holes in 35 mm film driving a numeric keyboard. The first computer in Harvard, "Mark 1" with a plug-in keyboard, measured 17 m, weighed 5 tons and consisted of 750 000 components (Figure 6.1). John von Neumann in 1945 developed a calculator with steering, memory, and enter and exit functions ("von-Neumann-architecture"). The ENIAC (Electronic Numerical Integrator and Computer) for military use by Eckert and Mauchly needed the ENIAC-girls to handle 6000 switches. Every now and then when one of the tubes was broken, a time-consuming search and repair had to be performed. The breakthrough came in 1947, when the first transistor was constructed, which made computers much faster and much more durable. On that basis Eckert and Mauchly of Remington Rand Co. constructed the UNIVAC (Universal Automatic Computer) in 1951 and used it to predict Eisenhower's victory in 1952. International Business Machines (IBM) developed the first type 701 ("Defense Calculator"), with 76 in use in the USA in 1956. Data could be directly accessed on 50 discs with a capacity of 5 MB each without Hollerith cards by the RAMAC (Random Access Method of Acquisition). The first microchips (quoted as "the nerve cell of the century") came to the market in 1958. In 1963 IBM began selling the System/360 computer family with exchangeable processors that were based on the integrated circuits by Noyce (founder of Intel) and Kilby (of Texas Instruments). In 1958 the first microchips were based on germanium, which later changed to silicone.

In the meantime the ASCII American Standard for Information Interchange had been developed. Digital Equipment Co. (DEC) then produced the first PDP-8 minicomputer with a teletype writing machine with the so-called QWERTY keyboard (named after the arrangement of the keys). In 1965 Gorton Moore of Intel Co. predicted that chip capacity would double every 12 months; he would later correct his prediction to every 18–24 months and which 40 years later would still be true. Intel developed the first microprocessor 4004 in 1971 for the Altair computer 8008, for which Paul Allan and Bill Gates programmed BASIC as computer software for the microprocessor and founded their own company, called Microsoft. In 1976 and 1977 Wozinski and Jobs (Atari) constructed "the Personal Computer" Apple I and Apple II, running on BASIC. These were followed by the first IBM PC in 1981, which ran on Microsoft's MS-DOS instead of the former DOS (Disc-Operating-System) developed by IBM for

organization of hard disc, files and other functions. In 1982 the computer was nominated "machine of the year" as the most promising device. In 1968 Engelbart, presented via long distance communication to a meeting in San Francisco, "the mother of all presentations" – the invention of the first graphic man–machine interface ("Sketchpad"). This was the birth of computer graphics, which was followed by an x–y-position indicator for computer screens – the mouse of today. In 1984 Apple introduced the Macintosh computer and in 1985 desktop publishing software. After Sony brought the first CD-player for compact discs to the market in 1983, Apple also developed the CD-ROM (Read Only Memory) drive.

For the improvement of communication between the increasing number of computer users the Advanced Research Project Agency installed the first network, the ARPAnet, followed by the ethernet (PARC). The internet had already started with Ted Nelson's Hypertext "Xanadu" in 1974. When Berners-Lee at CERN formulated HTML (HyperText Markup Language) in 1989 and http (HyperText Transfer Protocol) for communication on the World Wide Web (www) in 1990 the foundations for today's communication highway were laid. J. Clark then invented the first Netscape Navigator Browser in 1994 to take advantage of this system. By 1995 the net had already more than 45 million users. Today computer technology seems far from reaching its climax. New systems using supraconductive chips for quantum computing are under development reaching unprecedented speed and storage capacities [1–4].

Then what impact does computer technology have on current bronchoscopy and what will its future aspects be?

The influence of technology on endoscopy

Endoscopy techniques have always been closely related to the development of technology. Natural sunlight, focused through water-filled round glass bottles were in use not only for inspection of body cavities through the support of specula from Greek and Roman times but also through handicrafts for illumination of their work ("cobbler's bowl"), well into the middle ages. Only after concave mirrors had been developed for collecting the sunlight [5] could the faint light of candles be focused via hollow tubes, the first "endoscopes" [6,7]. Desormeaux' gazogene light had a short episode before the introduction of the electric light bulb by Edison in 1989. With the additional introduction of cocaine as local anesthetic by Jellinek in 1884, von Mikulicz' and Kirstein's rigid metallic tubes for inspection of the esophagus were first applied as tracheobronchoscopes by Killian in 1897. These instruments remained state of the art with considerable modifications until well into the 1960s [8].

The true revolution came with the introduction of the flexible bronchofiberscope by Ikeda in 1966 [9]. From then on bronchoscopy not only spread rapidly beyond specialized centers all over the world but also induced a tremendous increase in ancillary technology such as lasers, photodynamic therapy (PDT), high dose rate brachytherapy (HDR), stenting, endobronchial ultrasound (EBUS), etc. Many of these techniques were already based on computer technology. New technologies were introduced with increasing speed: the color video camera by Ikeda and Ono in 1971, bronchoalveolar lavage (BAL) by Reynolds in 1974, hematophotofrin derivative (HPD)-fluorescence by Cortese, transbronchial needle aspiration (TBNA) by Wang, Nd:YAG laser by Toty in 1978, and Iridium-192 (Ir192) brachytherapy by Hilarss in 1979. The first real computerized bronchoscope based on video chip technology was also developed by Ikeda in 1987. Stents were developed by Dumon in 1989, autofluorescence (AF) by Lam in 1991 and recently EBUS in 1999 and electromagnetic navigation in 2002 [10]. Newer technology like the color chip instruments, magnifying zoom endoscopes and AF, as well as techniques under development like endoscopic optical coherence tomography (EOCT), μCOSM and navigation by man–machine interface, are completely based on computer technology. This will be especially true for many future techniques such as robotics and application of nanomachines by remote control. In the following paragraphs we describe the influence of computers on bronchoscopy with regard to the different aspects of imaging, steering,

energy transfer, navigation, intervention and communication. As the development in contrast to our general perception is not following a linear path but rather is increasing with exponential speed ("Moore's law"), the limits of already existing technology and future developments are floating and by the time this book is printed the future in many cases will have become reality.

The current revolution in technology, imaging and information processing will have a major influence on bronchoscopy within the next two decades. We will be able to visualize structures *in vivo* that up to now only the pathologist could see; we will reach anatomic structures that are inaccessible by the bronchoscope yet; we will treat diseases that are still the domain of surgeons, medical oncologists and radiotherapists. We will be able to communicate online worldwide, improving standards of patient care, teaching and finally even performing interventional procedures via networks. Due to the exponential growth of sciences like computer technology, nanotechnology and biotechnology these changes will come on very rapidly. Also, the new quality of these intelligent instruments will demand a new ideological and ethical discourse on the future of science in general.

Computer technology in imaging

As much as the bronchofiberscope revolutionized the art of bronchoscopy by providing access to peripheral bronchi, ease of application under local anesthesia, and contributed to its worldwide spread, with respect to imaging it was a step backward compared to the superior quality of rigid optics. The improved image quality of fiberscopes was accomplished with an increased number of ultrathin glass fibers for photo and video documentation; this was paid for by a considerable decrease in the diameter of the biopsy channel to maintain an acceptable outer diameter to the bronchoscope. Thus one needed two different instruments for high quality documentation of interesting findings and for biopsies. Today, however, the gaps in imaging technologies with regard to resolution, field of view and penetration are closing continuously with computer technology playing a key role, just as is the case with general imaging in medicine [11,12].

Videobronchoscopy

The introduction of the first videochip endoscopes promised to be a considerable improvement. In this technology the image is provided by a chip behind the lens system within the tip of the flexible scope and is transferred to a processor via a wire. Only illumination of the airways is still provided by glass fiber light guide bundles. However, these videobronchoscopes only provided black and white images as pixels could not be packed tightly enough on the chips to install the necessary number of RGB pixels. A color image is generated by secondary computerized image manipulation in the processor; an RGB filter rotates in front of the halogen lamp providing rapid alternating illumination of the bronchial system by light of corresponding color. The color image is created by calculating the intensity of the reflected light in each of the three color components. The time involved in the process of image buildup is short enough for it to become unimportant for routine bronchoscopy. However, during quick motions or if fluids or blood are flowing within the airways the processing can be too slow to follow those swift motions and the image starts to become blurred. In addition, illumination by different light sources such as blue light for AF bronchoscopy or application of the Nd:YAG laser can cause severe disturbance of the processor and collapse of the image. Also, there is a complete breakdown of the image during application of high-frequency (HF) techniques like electrocautery or argon plasma coagulation. Thus in these instances one usually has to resort to conventional fibertechnology.

The recent introduction of true color chip technology overcame the drawbacks as the RGB pixels on the chip provide a true color image that does not have to be recalculated by the processor. The images created by these instruments are very similar to those seen with the rigid telescopes and are capable of high quality video and photo documentation. The rapid progress in chip packaging has led to a dramatic decrease in size of previous analog to convert PC technology. Thus, currently, the smallest color video chips with 50 000 pixels in the tip of ultrathin 2-mm endoscopes measure only 1 mm. These provide access to regions out of reach for regular bronchoscopes, with a superior image quality compared to fiberscopes (Figure 6.2). One

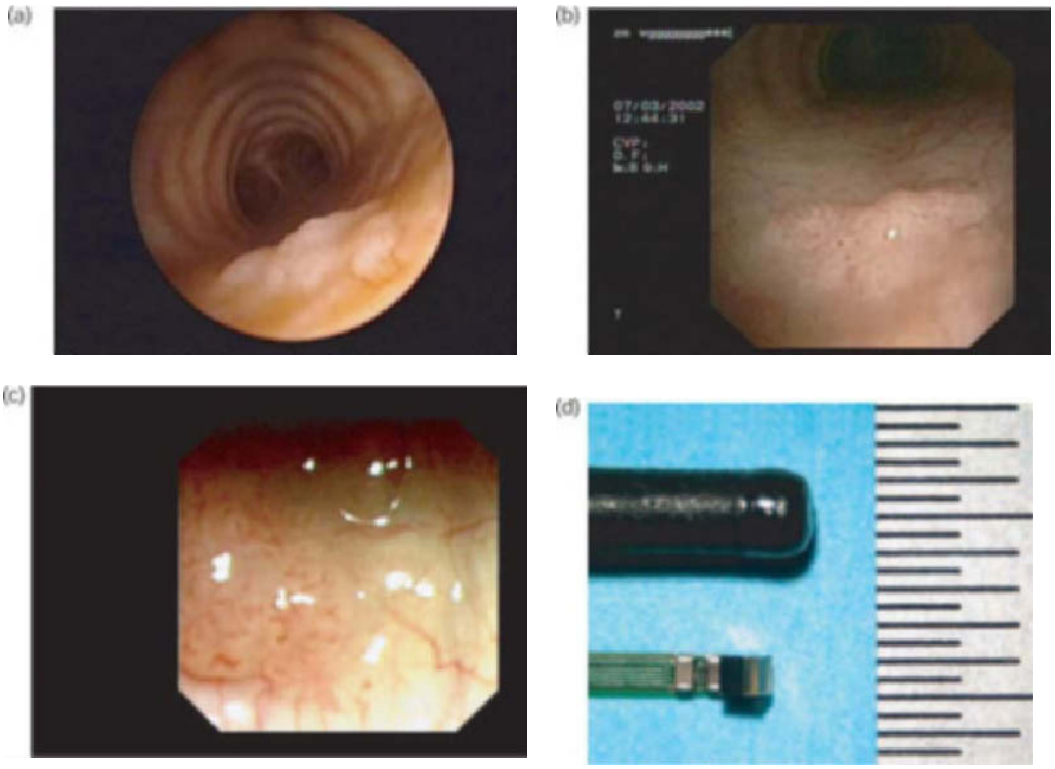

Figure 6.2 Comparison of different bronchoscopes: images by (a) rigid scope, (b) videoscope, (c) magnifying videoscope and (d) ultrathin videoscope. (Reproduced with permission from Olympus Co., Tokyo, Japan.)

of the most interesting features of the new video bronchoscope generation is post-processing. Image structure enhancement offers an as yet unknown image clarity of minute details that could never be detected by conventional techniques. Thus we are currently experiencing a closing of the gap between white light and AF bronchoscopy as we can see lesions in white light bronchoscopy (WCB) that had escaped detection earlier. These new generation endoscopes will play an important role in future programs for early detection of lung cancer.

Three-dimensional bronchoscopy

As miniaturization continues, it will enhance the incorporation of two objective lenses at the tip of the videobronchoscope at slightly different angles to one another providing a three-dimensional (3D) image. The combination of the digital imaging with computerized processing, in particular, will enhance endoscopic accuracy in objective measurement of longitudinal extent as well as square area of endobronchial lesions. Further combination with *laser probes* for accurate measurement of diameter and length of stenoses for objective documentation before and after treatment will serve as the basis for manufacturing individual stents. In this technique surface rendering of the airways by a circular laser image is fused with the video image for 3D reconstruction [13–16]. As in computer tomography (CT)-based virtual bronchoscopy the reconstructed image can be viewed from different angles at 360° and from inside (Figure 6.3). Three dimensional imaging will be completed by 3D EBUS which not only clearly shows the surface of the airways but also deeper structures of the bronchial wall as well as the surrounding structures, such as lymph nodes, vessels, tumors, etc.

Image fusion

Computerized fusion of these images with the endoscopic image will provide completely new

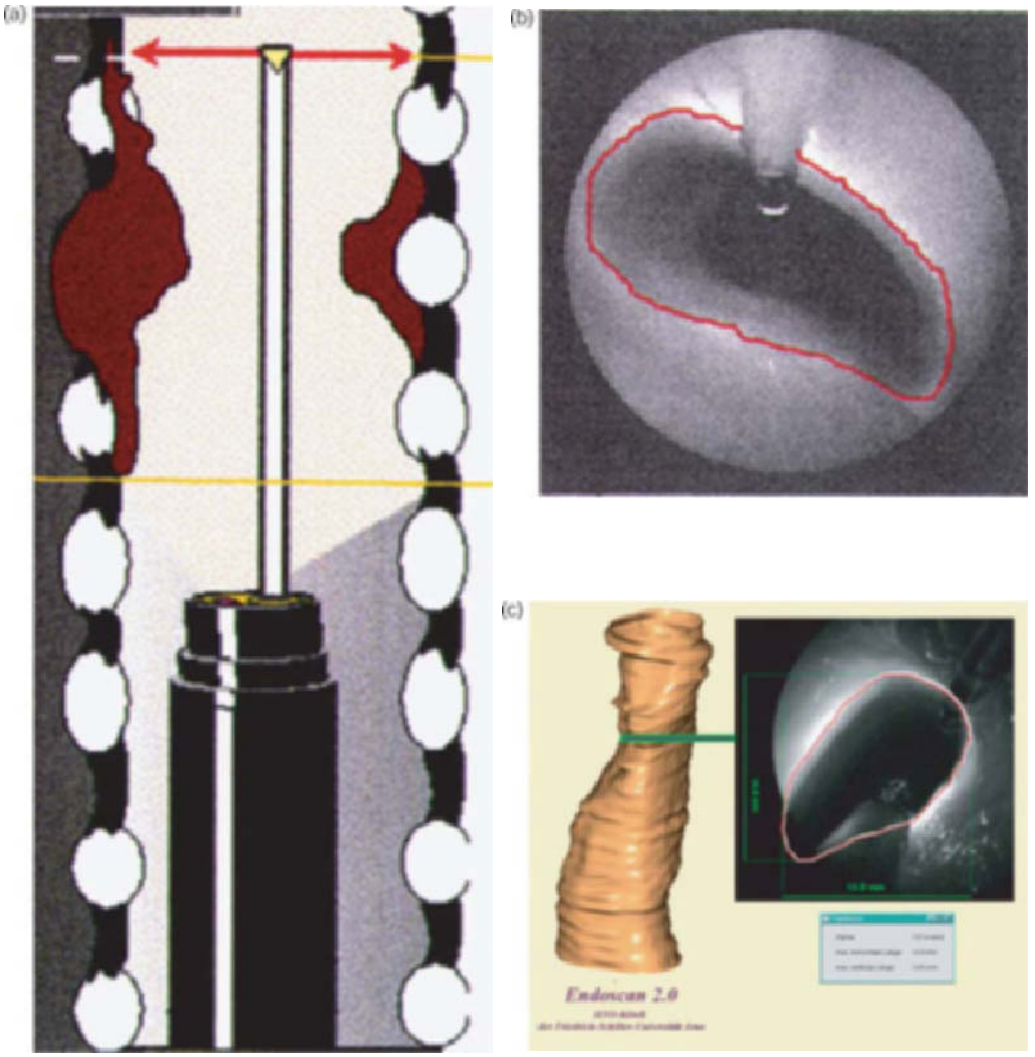

Figure 6.3 Laser scanning for measuring stenoses (Endoscan™). The laser probe is introduced via the flexible bronchoscope (a) and via a diffusor at its tip emits a radial laser beam (b). By pulling the probe through the stenosis and the fusion of the endoscopic image with the laser image a 3D reconstruction of the airways can be performed (c). This is also possible for functional imaging during breathing maneuvers. (Reproduced with permission from A. Müller.)

dimensions in imaging, much more accurate than CT-based virtual bronchoscopy as the resolution will be much higher and all the layers of the bronchial wall and surrounding structures can be clearly differentiated without the need of arbitrarily marking boundaries between anatomical structures (Figure 6.4). Also artifacts by secretions will be excluded and motion due to breathing and pulsation of vessels can be visualized. The greatest advantage, however, is real time true color imaging, tactile force impression and the possibility of acquiring bioptic material.

Monitoring by head-mounted display

Currently the images from different sources can be simultaneously observed on separate monitors, sometimes on picture-in-picture design (Figure 6.5). True 3D impression however, is only provided if the eyes get separate individual

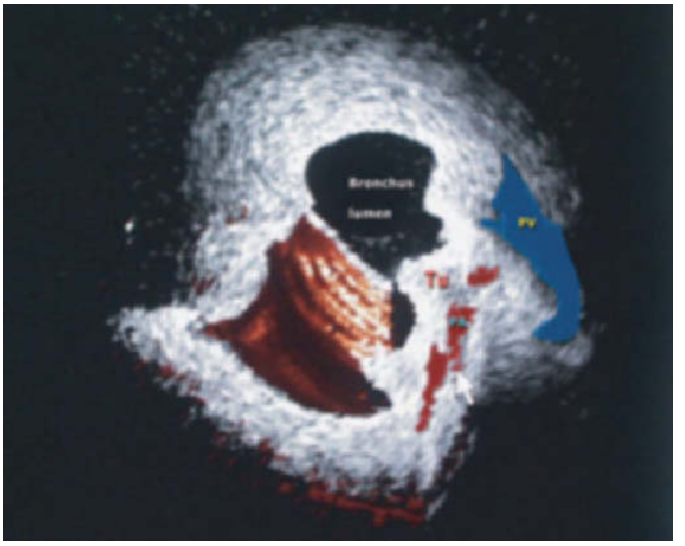

Figure 6.4 3D reconstruction by fusion of endoscopic and ultrasonic image of the airway. The mucosa within the bronchus lumen can be seen simultaneously together with a cross-section of the bronchial wall, showing a penetrating tumor (TU) and its relationship to the surrounding structures in the adjacent mediastinum, especially the pulmonary artery (PA) and pulmonary vein (PV).

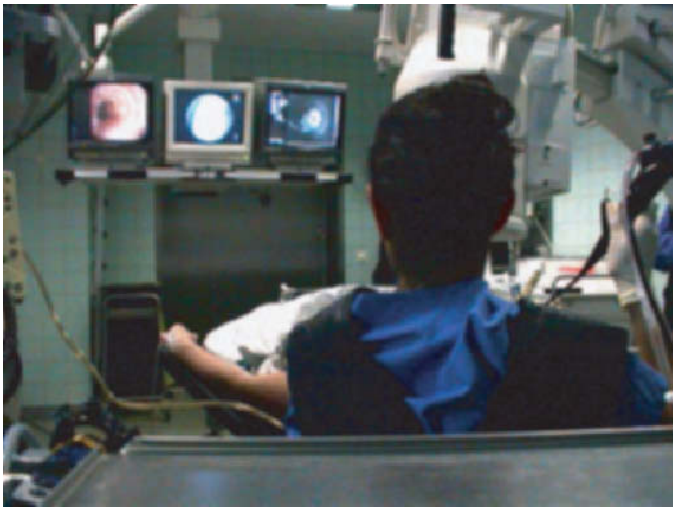

Figure 6.5 The images of different sources can be simultaneously observed on three monitors (from left to right: videobronchoscope, fluoroscopy, endobronchial ultrasound).

information. Two miniaturized personal operation monitors on a helmet, with head-mounted displays (HMDs) provide improved 2D or 3D images and free the hands of the interventionalist. By wearing the same device, staff personnel can follow the procedures closely. Different image settings can be activated by voice command or by remote control also in picture-in-picture mode, so multiple video sources can be simultaneously displayed on one monitor.

Endoscopic magnetic resonance tomography (EMRI)

The development of small coils for endoscopic imaging of the tracheobronchial system by magnetic resonance imaging (MRI) has not yet reached the stage of development for experimental investigation. The reception antenna of the MRI imaging endoscope will receive signals of extremely high resolution of the mediastinal structures, much superior to conventional MRI technology. It remains

open how integration of this technology will add to imaging procedures.

Magnifying bronchoscopy

Chip endoscopes with an integrated microactuator of 2 mm outer diameter (steered by a computer-controlled piezoelectric device) to operate a microscopic lens system in front of the chip can expand the view beyond the visible magnification from normal up to 100×; this is possible by adding zoom technology to endoscopic microscopy and it can provide visualization of structures up to now unrecognizable by conventional bronchoscopes. Analysis of the microvascular structure of small lesions by these instruments may prove useful for the assessment of their benign versus malignant nature. The process of tumor-driven vascularization causes an irregular pattern of structures making them more identifiable. *Computer-assisted pattern analysis* of the vascular structure of the bronchial mucosa could become an important addition to early detection and classification of malignant and pre-malignant lesions [17].

We had the opportunity of using a rigid bronchoscope with even higher magnification (Macrovision®, Wolf, Knittlingen, Germany) by which we could observe the motion of the red blood cells through the capillaries in normal and in pathological conditions. It still remains to be seen whether this instrument will provide new insight into pathologies and add to diagnosis.

Microconfocal scanning microscopy

With microconfocal scanning microscopy, (**μCOSM**) bronchoscopy has reached the cellular level. The system consists of an extremely miniaturized endoscopic laser scanning microscope, in which two mirrors driven by electrostatic actuators are built into one chip at the end of the endoscope. The laser light from an optical fiber is sent through a pinhole in a rotating scanning mirror and focused by a lens onto the tissue. The reflected light is collected by the optical fiber and reconstructed by computer technology to an image of up to 800× magnification. The resolution allows visualization of structures even within individual cells. In experimental studies malignant cells looked clearly different from benign cells (Figure 6.6). Even if the bronchoscopist were not to become the pathologist, by connecting the pathologist via communication lines *in vivo real-time pathology* will guide bioptic and therapeutic procedures in future [18,19].

Narrow band imaging

Conventional bronchoscopic imaging essentially makes use of the reflection of composite light from the upper layers of the airway lining. Imaging results from a complex summation of light reflection, scattering and absorption which varies in intensity according to the difference in wavelengths. Thus, penetration into tissues increases according to wavelength from violet to red. Blue light (~400–450 nm) is reflected by the superficial layers of the mucosa and submucosa, whereas green and yellow (~450–550 nm) penetrate more deeply and red light (~550–650 nm) penetrates the farthest into the tissue. Narrow band imaging takes advantage of these properties separating bands of different wavelengths by filtering out all other colors. Thus by observation under light of different wavelengths the image can be selectively focused on different levels of the bronchial wall, from the very superficial layers by blue light, intermediate layers by green color to deeper layers under red light (Figure 6.7). With this technology visualization can be performed on the cellular structures of the mucosa and submucosa or vascularity of the airway [20].

Autofluorescence bronchoscopy

Observation of the bronchial wall by illumination with blue light has become a well-established technology for early detection of malignant and pre-malignant lesions. This technique takes advantage of the fact that a proportion of the blue light excites so-called chromophores. The chromophores are contained within the layers of the submucosa and to our observation especially within the connective tissue of the elastic fiber bundles and of the perichondrium, which covers the internal surface of the cartilages. By filtering out 90% of the reflected blue light and just leaving enough to recognize the structures, a faint greenish fluorescence image can be observed. Pathological structures such as inflammatory reactions, granulomas and scars, but

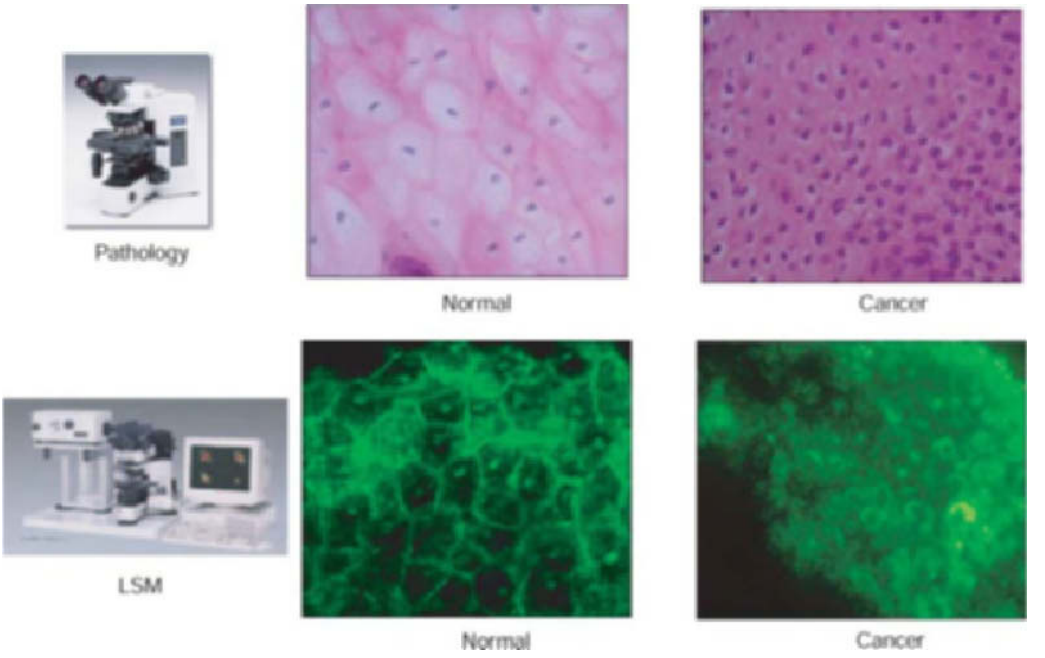

Figure 6.6 Microconfocal laser scanning microscopy (μCOSM) provides images of cellular structures (lower row) that compare to conventional microscopy (upper row). The images are taken from normal esophageal mucosa and esophageal cancer. Data on endobronchial application are not yet available. (Reproduced with permission from [19] and Olympus Co., Tokyo, Japan.)

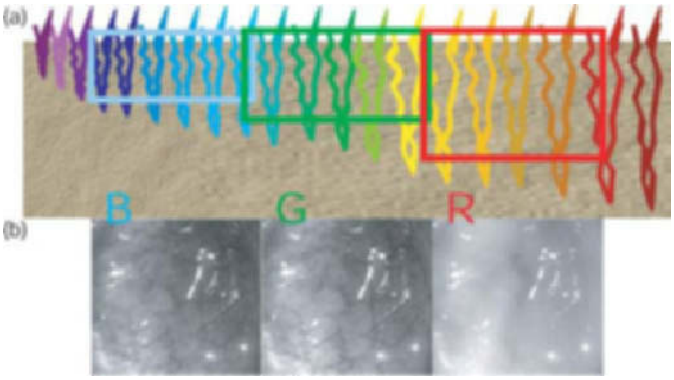

Figure 6.7 The diagram shows the difference in penetration from shorter to longer wavelengths (i.e. blue [B], green [G] and red [R] light) (a) and the corresponding images of the vascular structures in different layers of the bronchial wall (b). (Reproduced with permission from A.A. Obraevsky *et al*. Lasers Surg Med 1992 and Olympus Co., Tokyo, Japan.)

especially dysplasia and malignant lesions alter tissue visualization by changing the content of chromophores or by obliterating the transmission of the autofluorescent light to a darker reddish-brownish discoloration (Figure 6.8). Whereas the first devices needed chip cameras for high power computerized enhancement of the faint fluorescent light, some sources today allow observation with the naked eye via rigid bronchoscopes and flexible instruments. The latter remain fiberscopes to date, but as computer chip technology has been developing so quickly the first digital AF bronchoscopes are coming to the market.

As the AF of normal mucosa is very different from benign lesions and even more so from malignant ones, attempts have been made to quantify these differences by *computerized analysis* of signals of the different wavelengths. The superposition of the acquired signals is depicted as a spectrogram, which should show significant differences

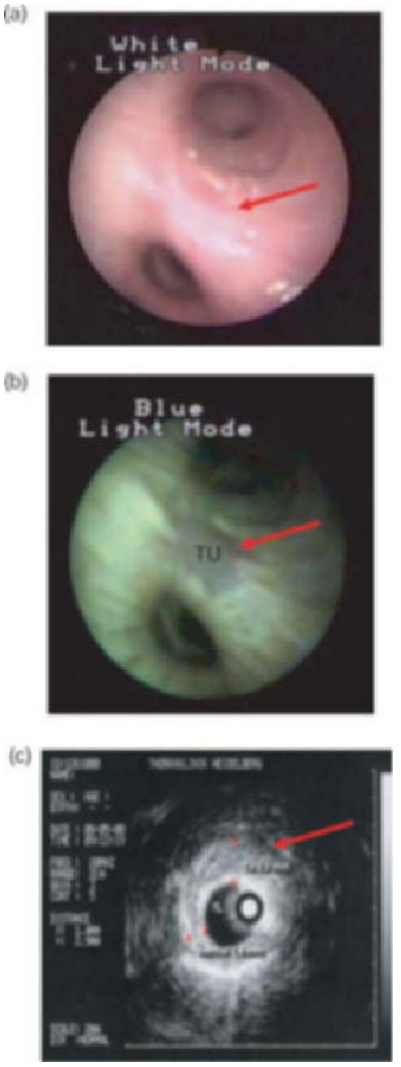

Figure 6.8 Autofluorescence (AF) and endobronchial ultrasound (EBUS) for detection and local staging of early bronchial carcinoma. By white light bronchoscopy (WLB) a faint discoloration is seen on the middle lobe carina (a). Autofluorescence (D-Light™) system, Storz Co., Tuttlingen, Germany) clearly shows a bluish discoloration at the site of the lesion (b) and by the 20-MHz miniature ultrasound probe (Olympus Co., Tokyo, Japan) the intramural extent of 3 mm and limitation within the confinements of the bronchial wall can be exactly assessed (c).

for benign and malignant lesions. First results with this technique have been quite promising and with increasing power and sensitivity of computer cameras and calculating programs automated detection including tissue differentiation seems feasible [21–23].

Light elastic scattering spectroscopy

In this white light technique the relative intensity of photons, which are reflected from different tissues without changes in their wavelength, is analyzed. The penetration of light scattering spectroscopy can penetrate the mucosa of the airway and extend into the submucosa. Changes in tissue composition on a cellular level such as concentration of nuclei associated with changes in density and size of the structures that are scattering the photons. For light elastic scattering spectroscopy (LLS), less expensive white light sources yielding strong signals in real-time can be used. The disadvantage of this technology is the small surface area that can be scanned by the probes. In the first clinical experiences, significant differences between dysplastic and normal epithelia could be observed.

Raman spectroscopy

Whereas in WLB imaging the photons that create an image are reflected without change in energy and wavelength (elastic scattering), Raman spectroscopy makes use of inelastic scattering of photons, where the photon's energy is changed and the light is shifted to a lower frequency, i.e. longer wavelength, by applying a spectral analyzer. As molecular bonds possess specific patterns in the spectrum, the molecular composition of tissues can be determined by Raman spectroscopy [24,25]. Since premalignant and malignant tissues are accompanied by changes in biochemical composition, Raman scattering could become a useful diagnostic technique in differentiating those lesions. Currently the technology is still under investigation as the signals are too weak for real-time *in vivo* imaging and the whole spectrum is too complex for detecting subtle changes by conventional techniques. This is why sophisticated complex computerized component image analysis and artificial neural networks and signal enhancement by application of metal nanoparticles are currently under investigation.

The three techniques (AF, LSS and Raman spectroscopy) can be combined (called tri-modal

spectroscopy) which in an experimental setting resulted in separating different grades of dysplastic epithelium from normal tissue.

Endoscopic optical coherence tomography

Whereas the above technologies serve imaging of the internal layers of the airways to a depth of sub-millimeter range, additional instruments allow deeper insights into structures of the bronchial wall. In endoscopic optical coherence tomography (EDCT) a low coherence laser light source is built into the tip of a catheter or the endoscope and a detector collects the images that are reflected by a reference mirror. The interference image is demodulated and processed by a computer [26–30]. The spatial resolution of this new imaging technique is 10–20 μm; depth of penetration is 2–3 mm. With EOCT mucosal structures, mucus glands, submucosal vessels and connective tissue layers can be clearly differentiated (Figure 6.9). Adding a Doppler function to EOCT allows local blood flow velocities to be assessed, providing information on regional microcirculation. How this will add to the information that we can obtain by HF EBUS is yet to be seen.

Endobronchial ultrasound

This new technology was commercialized in 1999 and opened a new dimension by expanding the bronchoscopist's view beyond the visible, closing the gap in penetration of optical technologies [31].

Since 1880 (J. and P. Curie) it has been known that by exposing certain crystals to alternating current, mechanical oscillations can be excited and vice versa. These oscillations can pass surrounding structures as waves (the principle of the loudspeaker). It is also recognized that the sound waves can cause crystals to emit electric current. Crystals used for these transformations are called transducers. The transducers send alternate short directed impulses and in the intermission, function as receivers for the ultrasonic waves reflected by different biological tissues. The signals are transformed to electrical impulses for image production. For this transformation further processing of the signals is necessary. By this processing the intensity of the reflected signal (echodensity) is represented by its brightness on a black and white screen and the local position of a structure is calculated based on the time gap between sending and receiving of the reflected signal. The ultrasonic image is a composite of reflection, attenuation, dispersion, thermal transformation, etc., which are

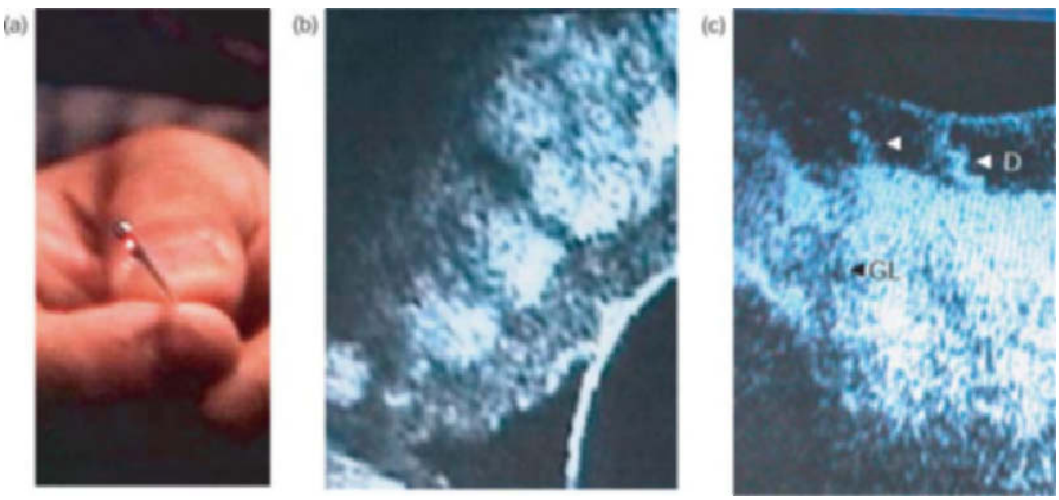

Figure 6.9 The catheter of the endoscopic optical coherence tomography (EOCT) probe has a small rotating light source at its tip and can be introduced via the biopsy channel of a fiberscope (a). The example demonstrates the different superficial layers of the skin at a finger tip (b). Higher magnification shows a sweat gland (GL) and two ducts (D) penetrating the skin to the surface (c).

dependent on the specific properties of different tissues with respect to their individual resistance (impedance).

Medical diagnostic ultrasound waves have frequencies between 2 and 20 MHz and wavelengths from 0.8 to 0.15 mm. The axial resolution of the image is dependent on the wavelength, which are usually 2–3 undulations. Lateral resolution depends on the width of the impulse and rises with the frequency, whereas depth of penetration reduces. As attenuation of the sound wave within the tissue is considerable the reflected signals have to be enhanced in accordance with the time (i.e. the distance) they need to return to the receiver (the time gain compensation or TGC). Within the processor the signals are first stored and then transformed into image lines to be presented as pixels for video signals. By further preprocessing, special parts of wave spectrum and borderline structures can be enhanced in order to provide improved image quality. By post-processing the gray scale can also be adjusted.

For detailed analysis of the bronchial wall we prefer US-probes of 20 MHz equipped with a balloon catheter for contact. Image resolution is well below 1 mm and penetration of up to 3–4 cm is attainable. By analyzing the structure of the bronchial wall with EBUS we were able to improve the accuracy of diagnosis of early malignant lesions considerably [32]. EBUS is the only current method for exact staging of early lung cancer [33]. This method has also significantly improved the results of TBNA of mediastinal lymph nodes (EBUS guided TBNA) in our hands. Differentiation of infiltration of the bronchial wall versus impression by external lesions is only possible by EBUS, which is most important for the decision for surgical procedures. Peripheral lesions can be approached by EBUS as accurately as through fluoroscopy, thus preventing radiation exposure. Computerized texture analysis of these lesions based on the ultrasonic image proved a highly reliable assessment of their benign or malignant nature (Figure 6.10). The combination with semi-automatic steering devices will enhance therapeutic approaches for the diagnosis or destruction of peripheral lesions via the transbronchial route. EBUS proved valuable in interventional bronchoscopy, especially in evaluation of peribronchial vascular structure, by avoiding perforation with mechanical devices, lasers or brachytherapy [34].

Current experiences with the new integrated hybrid chip ultrasonic bronchoscope, called the "puncture bronchoscope," carry an array of electronic transducers at the tip, providing their superiority in the imaging of the mediastinal structures. Penetration of the 7.5 MHz sound waves is much improved. The integrated biopsy channel allows EBUS-controlled needle biopsy of lymph nodes and lesions under direct visualization. Color

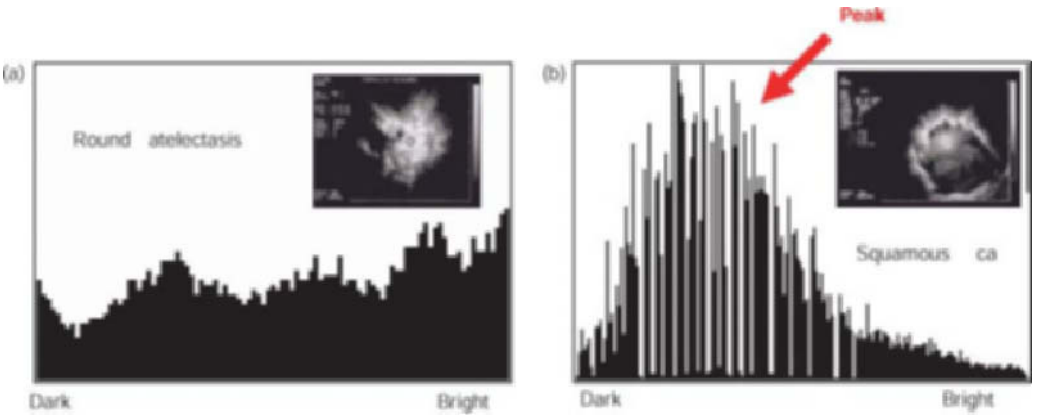

Figure 6.10 Computer-assisted analysis of ultrasonic images. On the scans of ultrasonic images of a benign (a) and a malignant (b) lesion the number of pixels of different brightness are calculated by a computer program (Picture Publisher™). Whereas the benign lesion shows a homogeneous distribution from dark to bright signals, the malignant lesion shows a typical peak in the dark range, which is highly significant.

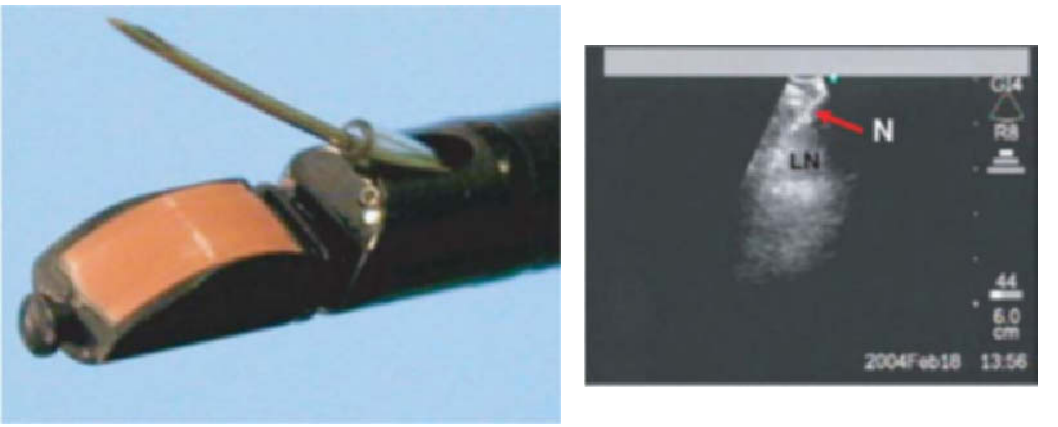

Figure 6.11 The ultrasonic bronchoscope with linear electronic transducers at its tip (Olympus Co., Tokyo, Japan) allows direct visualization of the needle (N) for guidance of transbronchial needle aspiration of mediastinal lymph nodes (LN).

Doppler function has been added, greatly improving imaging and functional assessment of vascular structures (Figure 6.11).

One of the most appealing features in EBUS is its future ability for navigation and control of interventional bronchoscopy beyond visible areas. Three dimensional EBUS will improve assessment of tumor volume as a basis for dosimetry in PDT and brachytherapy (HDR). Fusion with the endoscopic image will improve orientation and interdisciplinary planning for treatment dramatically. EBUS will be useful for real-time steering of instruments into deep organs and for controlling the effect of therapeutic procedures such as radiofrequency ablation or microwaves by change of the impedance due to drying of the tissue. High-frequency intensified focused ultrasound (HIFU) will become an efficient tool for destruction of pathologic tissues. By this technique, tissue is destroyed noninvasively at a distance from the probe by focusing the HIFU transducer on a limited portion of the tumor.

Immunophotodiagnostic bronchoscopy

This technique uses the conjugation of tumor specific antibodies with florophore dye as a contrast agent, which might enhance the fluorescence contrast between tumors and surrounding normal tissue [35]. Prerequisites for obtaining useful images are specific antibodies, availability of near infrared light emitting fluorophores and high-sensitivity digital cameras for visualization of the very faint fluorescence that can be detected through millimeter thicknesses of tissues. The antibodies can also be directed against tumor specific enzymes (enzyme-sensing probe). However, as large amounts of injected conjugated antibodies have to be applied; host–immune responses may be a major obstacle.

Functional imaging

New procedures of *in vivo* imaging of functional status such as ciliary beat, local bronchial and pulmonary interstitial inflammation, contraction of the bronchial muscles, bronchial and mediastinal blood flow and tracheobronchial airflow will generate new insights into pathomechanisms and generate new technologies for noninvasive local treatment, such as controlled radial destruction of bronchial muscles for treatment of asthma (Alair™) and plugging of bronchi for treatment of localized emphysema (Emphasys™) and management of bronchopleural fistulas.

With these technologies under development, bronchoscopy is currently evolving into one of the most important tools for scientific research in pulmonary medicine, molecular biology and clinical oncology.

3D-imaging and image fusion

Two miniaturized personal operation monitors on HMD will enhance procedures by providing

improved 2D or 3D images and freeing the hands of the interventionalist. By wearing the same device, staff personnel can follow the procedures closely. The different imaging procedures can be activated by voice command or by remote control in picture mode, so multiple video sources can be displayed simultaneously on the monitors. By overlaying different image sources simultaneously, such as the endoscopic video image and the ultrasound image, the bronchial lumen, the structures of the wall and the surrounding structure of the mediastinum can be visualized parallel in real time, thereby enhancing diagnostic and therapeutic procedures. Also overlaying the virtual bronchoscopy image from 18 line spiral CT reconstruction over the actual bronchoscopic image and even fluoroscopy might provide improved navigation into peripheral structures. The overwhelming amount of information, however, might demand computer-assisted analysis for steering and navigation.

Computer-assisted image analysis

The eye of the well-trained bronchoscopist can take up an incredible amount of information and intuitively differentiate abnormal from normal structures. The complex information is amongst others derived from mucosal color tone, such as redness or whiteness, from regular or irregular vascularity, smoothness or roughness of the mucosal surface, etc. Those alterations, however, can be very subtle and easily escape the not-so-well trained eye, as has been demonstrated in early cancer detection of the colon [36]. Computer-assisted numerical analysis of different features of the image, such as colorimetric value, contrast, pattern regularity, complexity, extent in length and area etc., might be useful.

The first such attempt was made by analyzing the differences in fluorescence images of normal, suspicious but benign, and abnormal malignant lesions. Fluorescence bronchoscopy is much more efficient in detecting preinvasive lesions than white light examination, but its specificity in determining malignant lesions is comparably low. Therefore in the future, quantitative fluorescence imaging or even combined fluorescence–reflectance imaging may prove useful to improve specificity.

Computer-assisted calculation of microvascularity in preneoplastic lesions was recently published. Using the images of a new high magnification bronchovideoscope a significant difference in vascularization was observed for normal mucosa as compared to chronically inflamed and preneoplastic mucosal alterations. After computerized extraction and noise reduction on green images, areas of interest and vascular area ratios were determined and compared between sites of normal and abnormal fluorescence. The results indicated a statistically significant increase in vascular areas, considered to be correlated to the neovascularization processes in evolution of malignant lesions [17].

Benign and malignant lesions within the lung tissue differ significantly with regard to their internal ultrasonic structure which can be expressed in a complex multifactorial analysis of different features [37]. In a recent study we could demonstrate the usefulness of computer-assisted analysis of ultrasound images of peripheral lung lesions. Instead, we used a computer program for calculating the number of gray scale signals within a given area of interest. The resulting curves showed a consistent peak in the dark range of the gray scale for malignant lesions as compared to a homogeneous distribution in benign lesions which was highly significant [38].

If significant features can be recognized by computer-assisted image analysis the programs can be integrated into the computer program and can be shown online while the examination is in progress and diagnostic procedures for specimen sampling and even therapeutic procedures for destruction of malignant lesions can be performed more accurately [39]. Eventually, when integrated into feedback circles of automated machines they can even guide robots.

Optimal imaging technique

An optimized imaging technique should combine several features to be the ideal system. It should

1 work in real-time;
2 provide excellent diagnostic accuracy;
3 demonstrate wide mucosal area surveillance;
4 have sufficient penetration to deeper layers of the bronchial wall; and
5 be applicable beyond the visible airways in the periphery.

Ultimately, we are expecting a technology that, based on imaging, will provide guidance in locating optimal sites for targeted biopsies or even provide an optical biopsy, which based on immunophotodiagnosis will tell us which lesion has to be treated. Local accurate staging should provide guidance in locating the site and the depth for ablative interventions and will serve in monitoring the efficacy of endobronchial therapy.

Image transfer

Currently image transfer from the sources to videomonitors is taking over from direct observation of the image at the ocular on the proximal end of the bronchoscope. This needs a fixed position of the monitors so that all partners of the endoscopy team have an unimpaired view of the screen or else they will start suffering from health problems in their static systems due to malpositioning. HMDs are a considerable step forward as they allow free positioning of the observer's head independent of the location of the image source (Figure 6.12). However, they are still comparatively bulky and due to their being attached to the processor, freedom of mobility is still somewhat hampered. *Cyber spectacles* with wireless signal transfer from the source will be a definite step forward, freeing the staff's mobility completely from any attachment to computer hardware. When providing long distance connectivity the observer can even stay far away from the procedure and follow the activities. The next generation will be small laser projectors that transfer images not only from endoscopes but also from other sources directly onto the retina of the eye (retinal projection), www.microvision.com [40].

New interactive technologies

Steering mechanisms

Because of the need for advanced maneuvering a new steerable device with sophisticated eight-way wiring for 360° mobility has been designed, which is currently applied for steering the locatable guide in the SuperDimension/bronchus® system (Figure 6.13). As the new generation instruments will be steered increasingly by remote control, new sensors will assist in guiding endoscopes through the sinus passages of the body, at the same time causing less discomfort than manual steering maneuvers [41].

Optical sensors

Optical sensors function by computerized analysis of the endoscopic image. The computer checks whether the endoscope can be advanced in the desired direction and, if not, automatically redirects maneuvering by feeding the new data to the driving unit.

Tactile sensors

Tactile sensors control the forces used during insertion and assist in the steering of the endoscope.

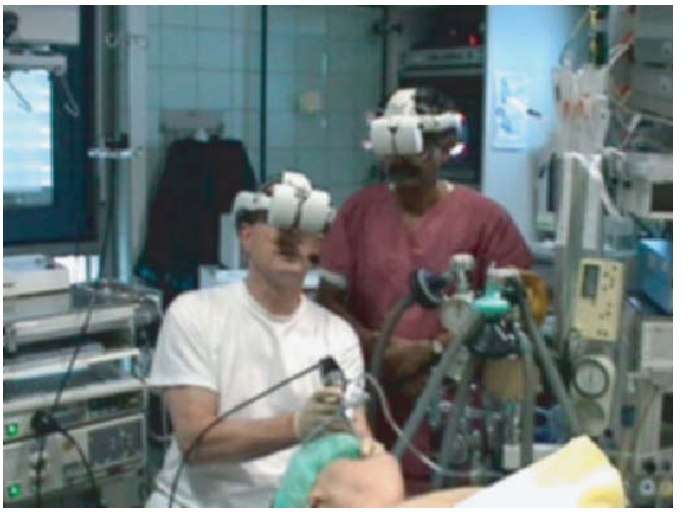

Figure 6.12 Head mounted device (HMD™, Wolf Co., Knittlingen, Germany). Two monitors are mounted on a helmet and provide two separate images on the eyes thereby creating a 3D image. Any observer wearing the device can also follow the procedure in 3D version.

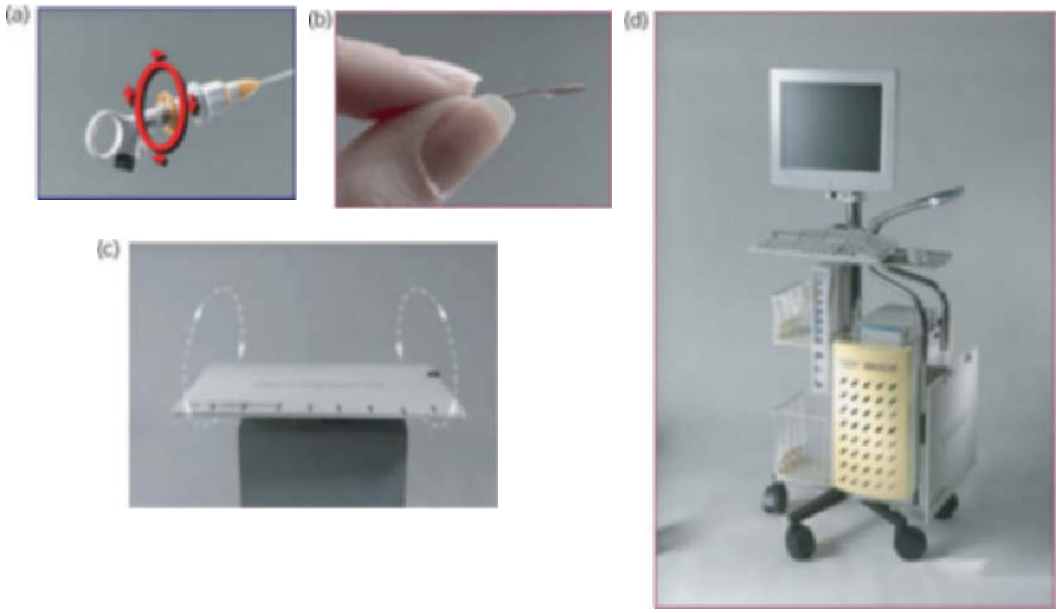

Figure 6.13 The SuperDimension bronchial system (SDBS™, SuperDimension Co., Herzliya, Israel) consists of a steerable guide (a), bearing an electronic sensor at its tip (b) that can be localized within a magnetic field around the patient's upper body, created by a magnetic board (c) that is placed on the examination table. The sensor is connected to a computer and can be followed on a three planar CT on the computer screen that is superimposed on the patient's real anatomy (d).

These sensors function like tentacles of snails in activating the motion device. If they detect some level of resistance during insertion of the endoscope, they induce deflection of the tip by either giving information to the endoscopist for manual steering or by activating shape-memory alloy (SMA) catheters or a remote control for detached endoscopes. Force feedback systems will be integrated into "intelligent" instruments such as forceps, needle, snare, basket or other probes that will give an artificial impression of the forces to the operator, who actually is no longer maneuvering these instruments directly by hand but by telemanipulators or even by joystick on a remote control panel via monitor guidance.

Neuronal sensors and robots

Most recent systems integrate chip technology and neuronal structures. In this technology, neurons are directly connected to computers or computer-driven machines. Manipulators therefore will be controlled no longer by hand (lat. *manus*) but by eye-trackers and brain-wave sensors. Brain-wave and neurochips will be wired directly to the digital worlds and control devices. This symbiosis between man and machine is a further step toward applied robot technology. True robots, however, will no longer need the interface with humans but will perform diagnostic and therapeutic procedures independently based on computerized feedback data. Humans will act only as standby to intervene by trouble-shooting if anything goes wrong [42–45].

Energy transfer

As the miniaturization of imaging and therapeutic instruments makes progress, interventional systems must be redesigned. This applies especially to steering mechanisms. The diameter of instruments are becoming so small that steering by conventional tendon-wire technology is no longer possible because of the increasing friction in complicated airways and the lack of rigidity of these instruments.

360° Steering mechanical catheter (locatable guide)

The first catheter based on conventional mechanics that can be selectively maneuvered in eight directions thus providing 360° motion freedom has been recently developed by SuperDimension™Co. It is attached to a sensor probe to approach peripheral lesions beyond visibility via the endoscope. The sensor is guided manually into the lesion by virtual navigation. After correct placement a catheter can be slipped over and after removal of the sensor it can serve as an "extended biopsy channel" for insertion of diagnostic and therapeutic tools (Figure 6.14).

Shape-memory alloy catheter

For this purpose a miniaturized active bending catheter has been developed, through which the miniaturized endoscope or instruments can be introduced. The bending mechanism is provided by shape-memory technology (SMA). Crystals of "smart" alloys like Nitinol (nickel–titanium) are arranged in a complex folding pattern that changes their internal structure by force or temperature. Wires made from these materials bend and unbend to a preset geometric configuration when heated by electric current. This process can be activated by remote control. The wires can be extremely thin, because they are actively bending and do not have

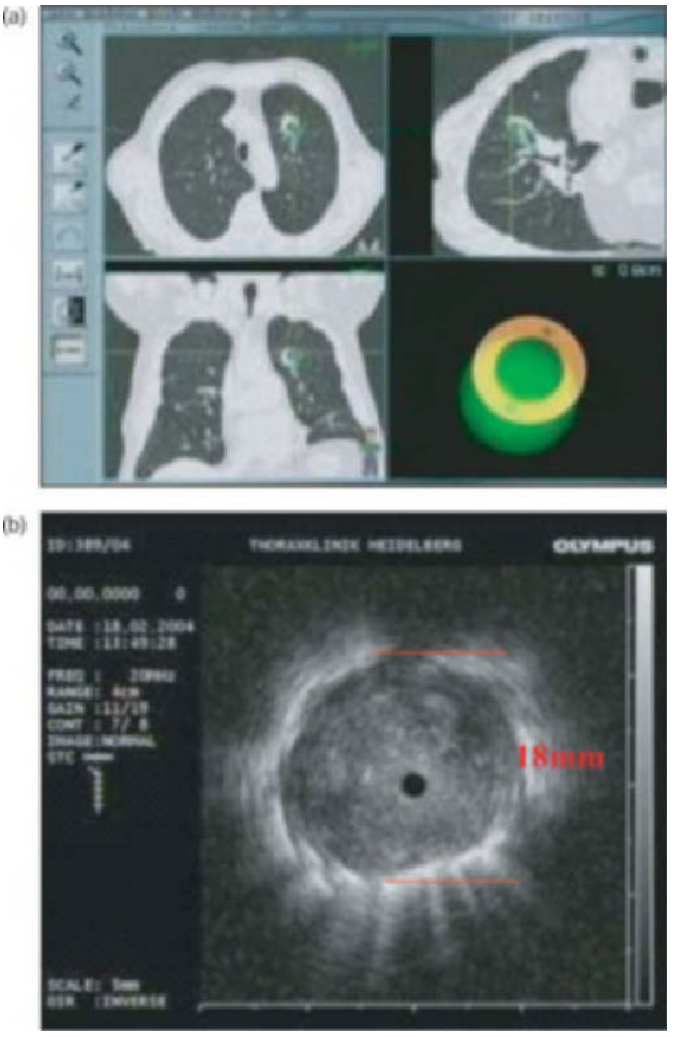

Figure 6.14 A sensor is navigated into an 18-mm peripheral lesion in the apical segment of the left upper lobe (a). The exact central position of the catheter and the size of the lesion is confirmed by introducing the endobronchial ultrasound probe (b).

to withstand stronger forces of traction. Catheters of extremely thin external diameter, below 1.5 mm, can be manufactured through which a 0.6-mm ultrathin endoscope or corresponding instruments can be inserted. Stabilization of these instruments can be achieved by insertion via biopsy channels of regular endoscopes ("mother–baby technique").

Capsular endoscopes

Recent concepts for future endoscopes abandon hand-guided instruments in favor of remote-controlled capsular endoscopes. The various functions of endoscopes such as ultra-small charge-coupled device (CCD) chip, miniature light source, micromanipulator, microsensor and signal transmission are integrated in a compact fashion. These capsular endoscopes have gained quite a bit of popularity in gastroenterology for the imaging of parts of the small intestine that are very difficult to access. Here they follow the route of the peristalsis and leave the body "per vias naturales." However, in bronchology, even after having been propelled by inhalation and steered toward the lesion by remote control on the basis of virtual bronchoscopy, they would still have to be retrieved by conventional bronchoscopy. Thus we do not expect capsular endoscopes to play a comparable role in bronchoscopy.

Navigation systems

Navigation of diagnostic and therapeutic instruments by conventional technology comprises endoscopic visualization, fluoroscopy, CT-guided maneuvering [46–48] and most recently EBUS-guided steering. The most favorable success rates in approaching peripheral lesions beyond visibility by even the smallest bronchoscopes are 75–80% for skilled specialists and for the average bronchoscopist much less (50–60%). The success rate depends on imaging quality on one hand, but much more so on the individual manual skills of the bronchoscopist. Thus a considerable number of lesions have to be diagnosed by more invasive radiological transthoracic or even surgical approaches. As far as curative endo- or transbronchial intervention is concerned, reliable methods, independent of individual factors, become an absolute necessity.

Electromagnetic tracking device

The most recent development is navigation by electromagnetic field navigation method, the SuperDimension™ system. For this purpose the patient is placed in a low power magnetic field that is generated by a location board connected to a location processor and a location amplifier. A locatable guide and locatable sensors on the patient's body are connected to the tracking device. The electronic circuitry generates low frequency current for the location board and calculates the location and position of the sensors, which are found within the low frequency magnetic field of the location board. A PC-based image processing workstation processes the sensors' position and orientation data and correlates the data with CT images. The locatable guide is maneuvered by the 8D steering mechanism toward the lesion. The target is acquired from the pre-interventional CT image, registered on the current position of the patient's body and marked on the workstation's display. The locatable guide, which incorporates a location sensor at its tip, is then maneuvered accurately toward the lesion in 3D on the screen (Figure 6.13). After first successful animal experiments we investigated the reliability of this new device for navigation in a pilot study. In another study we examined the accuracy in reaching targets within the central airways as compared to videobronchoscopy and could find a mismatch of 2.4 mm. Based on the electronic sensor technology, hybrid instruments can be conceived by integrating steerable optical instruments with needles, brushes, curettes and therapeutic applications [49,50].

Currently the locatable guide is manipulated by the bronchoscopist's hand. However, as a virtual path can be created by segmentation of the bronchi from the surrounding structures on the planning CT, this information can be fed into the computer. Thus by connecting the sensor to a small motor that is driven by the computer, there is automatic navigation toward the target. Navigation is controlled by optical and tactile sensors and the bronchoscopist is on standby to prevent complications and after reaching the target to induce the diagnostic and therapeutic procedures. Thus advanced electromagnetic navigation will be the first man–machine interface technology as an intermediate step toward robotics.

Robotics

All current man–machine technologies are based on manipulators functioning on the master–slave principle. Manipulators are steered by humans and motion is transferred to endoscopic instruments. As this can be done by remote control, it does not matter whether the physician is in the endoscopy suite or in a remote place. True robots ("robota," Czech for slave work) would replace human perception and flexibility by artificial sensors and computer programs. Data retrieved from virtual bronchoscopy and endoscope 3D laser scanning are fed into the computer's memory and the robot will perform a procedure based on optical and tactile sensors that by difference in resonance frequency can discriminate different tissues. It is expected that by eliminating tremor via filters and preventing fatigue due to stabilizing endoscopes in awkward positions and by precise continuous processing, mistakes during the operation might be prevented. However, mistakes by planning are still possible. Visions of autonomic computing as basis for true robots are beginning to be implemented in large-scale computers: (a) self configuration by contacting other systems for maintaining function in case of interruption of data flow; (b) self protection against viruses, intrusion and other safety risks by intrusion detection; (c) self optimization in distribution of capacities according to demands for calculation; (d) self curation in solving technical problems that could shut down the robot. The computer makes diagnoses and decisions and by the conclusions takes measures to overcome problems and maintain its function, very much like the autonomous neural system. By connecting to local or internet-based networks the data are provided to an administrator who can eliminate the source of malfunction and also the computer can download drivers and updates of antivirus programs. Once these features are implemented, complete breakdown of the computer system or loss of data can be avoided, especially if computers share resources via worldwide stable networks. In addition final control still lies in the hands of the administrator who gives the tasks and sets priorities [51–56].

Virtual bronchoscopy

One of the current concepts is based on integration of reconstructed 3D CT imaging (virtual bronchoscopy) with videobronchoscopy. The bronchoscopist can simultaneously observe the bronchoscopy image and navigate the instrument along the path shown by virtual bronchoscopy by monitor control and image in image insertion technology. This technique is currently under investigation and it remains to be proved whether loss of imaging control caused by artifacts such as congestion and complete obstruction of airways by sticky secretions may interfere with maneuvering. By applying virtual bronchoscopy to electromagnetic navigation, we have seen that, especially in severely deformed airways, in airway obstruction by endobronchial lesions, and after previous surgical procedures, the virtual image can be very misleading and navigation based on these data can be extremely difficult [57–59].

Virtual bronchoscopy is a key future technology for maneuvering endoscopes through the airways and for the planning and teaching of interventions. Since the introduction of electron beam CT scanners data acquisition has become fast enough to gain high resolution images of the whole thorax within seconds and even record the motion of one single breathing cycle. We applied this technology in several cases for analyzing the location and extent of central airway collapse. Modern multidetector CT scanners provide data in high speed and high resolution that allow accurate visualization of small lesions within the airways. It has proved so useful in the assessment of central airway stenosis that individualized stents can be produced (Figure 6.15).

Transbronchial needle aspiration of mediastinal lymph nodes can be performed more accurately than by conventional technique. Its place in detection of early lung cancer in the central airways is limited by a high false positive rate due to misinterpretation of secretions. Segmenting out the bronchial tree to extrabronchial structures is a major prerequisite for navigation of diagnostic/therapeutic tools and miniaturized endoscopes toward peripheral lesions within the lung. Since, there is currently, a vast number of small peripheral lesions that is detected in projects with low dose spiral CT, of which more than 90% are benign, which due to their size and location will easily escape CT-guided transthoracic needle biopsy and video-assisted thoracic surgery (VATS), we are convinced that sophisticated bronchoscopic

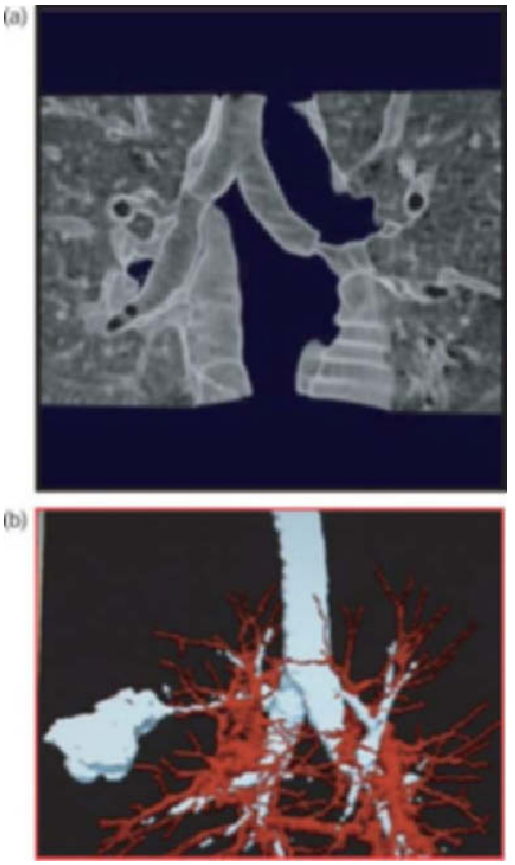

Figure 6.15 Three dimensional reconstruction of a thorax CT and rendering of the central airways demonstrating a postoperative stenosis at the site of an anastomosis (a). (Courtesy A. Ernst, Beth Israel Deaconess Hospital, Boston, MA, USA.) On virtual bronchoscopy the path leading to a peripheral lesion is calculated by rendering the pulmonary vessels and the bronchial tree (b). (Reproduced with permission from German Cancer Research Center, Heidelberg, Germany.)

methods navigated on CT-based virtual bronchoscopy are needed to avoid unnecessary surgical procedures or delay in diagnosis of cancer at an early stage. Integration of virtual bronchoscopic CT-derived images with color bronchoscopic images into a synergistical dataset might become another useful tool for early cancer detection [60–63].

Holographic touch panel

As is already the case in our unit for image controlling, steering of instruments will be controlled on touch panels that are integrated within the setting of light sources and processors. Usually these are not installed within the field of vision of the endoscopist. Thus either an assistant has to handle those instruments that afford continuous communication and distract the attention from assistance in the procedure or the bronchoscopist has to turn his or her attention away from the patient and the instruments, which especially in advanced imaging like EBUS and in interventions can cause considerable delay or even complications at worst. In addition, this affords unphysiological ergonomical body posture and frequently causes health problems for the endoscopy staff. By a recent new computer technology, holographic images of what would otherwise be the computer keyboard, keypad or touch-screen are projected into the air in front of the equipment, if desired at a considerable distance. An infrared detector scans the plane of those holographic images to detect the intrusion of a finger into the desired portion of those images, identifies which number or symbol has been selected, and transmits that selection from the equipment's internal software, in much the same way as pressing a button on an ordinary computer keyboard or keypad would [64]. Because there is no need to physically touch any hardware by using the HoloTouch, healthcare personnel can gain direct, reliable control of operating room equipment, where actuation and control must be indirect because computer keyboards cannot be effectively sterilized. Apart from the nontouch properties of this device, the keys, icons and images on the hologram can be arranged according to individual needs and the panel can be placed anywhere in the air in front of the bronchoscopist (Figure 6.16).

Interventional bronchoscopy

One of the topics currently gaining attention is application of interventional procedures in bronchology. This comprises not only safe application of interventional techniques but also training, documentation and communication. As the basis for planning of all interventions is detailed imaging of the anatomical structures all the computer-based techniques that we have described will have tremendous influence on further progress in diagnostic and therapeutic bronchoscopy.

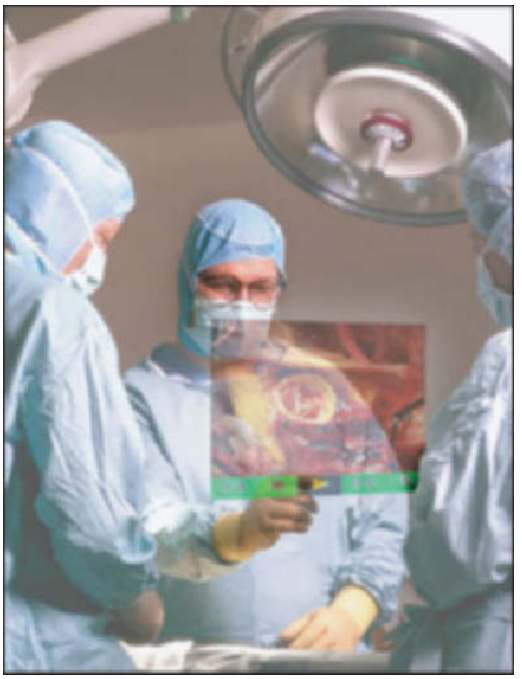

Figure 6.16 The HoloTouch™ panel can be placed anywhere in the room and can be handled without touching any hardware. Reproduced with permission from Holotouch Inc. [64].

Based on the results of computer-guided imaging diagnostic procedures such as TBNA and transbronchial lung biopsy (TBBX) are already being performed much more effectively. Also for planning of endoluminal high dose radiation by brachytherapy 3D imaging and volume rendering on EBUS images greatly improves dosimetry.

Real-time guidance of instruments are essential, especially when we are beginning *transbronchial therapy*. Thus transmural fine-needle injection of cytotoxic agents or of viral carriers for gene therapy into lesions adjacent to the central airways can be exactly customized according to the tumor volume. Injection ports, routes for placement and deposition volumes can be planned pre-procedure and the procedure itself can be controlled by computer assistance based on virtual imaging (Figure 6.17).

For exact navigation of therapeutic instruments into *peripheral lesions* such as laser probes, needles, HF electrodiathermy or HIFU-probes guidance by the electromagnetic tracking device is essential. Once the catheter is safely lodged within the lesion the sensor can be withdrawn and replaced by an ultrasonic probe. Computer-assisted analysis of the ultrasound image gives considerably reliable information on the nature of the lesion and supports decision for the best localization for obtaining biopsy specimens that can be analyzed by the pathologist via telepathology. Histology and volumetry being established, a therapeutic device can be installed and the therapy can be performed by computer-calculated application of energy for tissue destruction.

Endobronchial lesions will be destroyed after computer-assisted imaging and volume rendering, integrating intraluminal, intramural and parabronchial extent. Dosimetry for Nd:YAG-laser application or PDT will be individually calculated and correctly applied according to the virtual volumetry, avoiding damage to vital adjacent structures like great vessels or to the esophagus.

Parabronchial lesions within the adjacent mediastinum can be exactly visualized and approached by needle aspiration for diagnostic purposes. Under ultrasonic control, probes could be inserted and destruction of the lesions can be performed by exact dosimetry according to the target volume by radiofrequency ablation, cryotherapy or injection of liposomal encapsulated chemotherapeutic agents.

Peripheral leisions, once they are accurately approached by dedicated navigation systems and therapeutic tools such as radioablation probes, cryoprobes and lasers that can be safely lodged within, could be treated with a potentially curative intent. First attempts have been made via CT guidance of brachytherapy catheters. We are currently performing a pilot study, introducing brachytherapy probes via catheters that are placed under electromagnetic guidance and EBUS control. The catheter is left in place for a week and fractionated high dose radiotherapy is applied every other day. The results seem promising so far and up to now we have not observed any complications.

A completely new generation of miniaturized instruments is showing up on the horizon, the *nanomachines* ("dwarf" machines). The functional elements a few millionths of a millimeter in size are built from molecules or even atoms according to computerized design. With these instruments, surgical procedures will be performed on a cellular or even molecular scale. Eventually the devices will

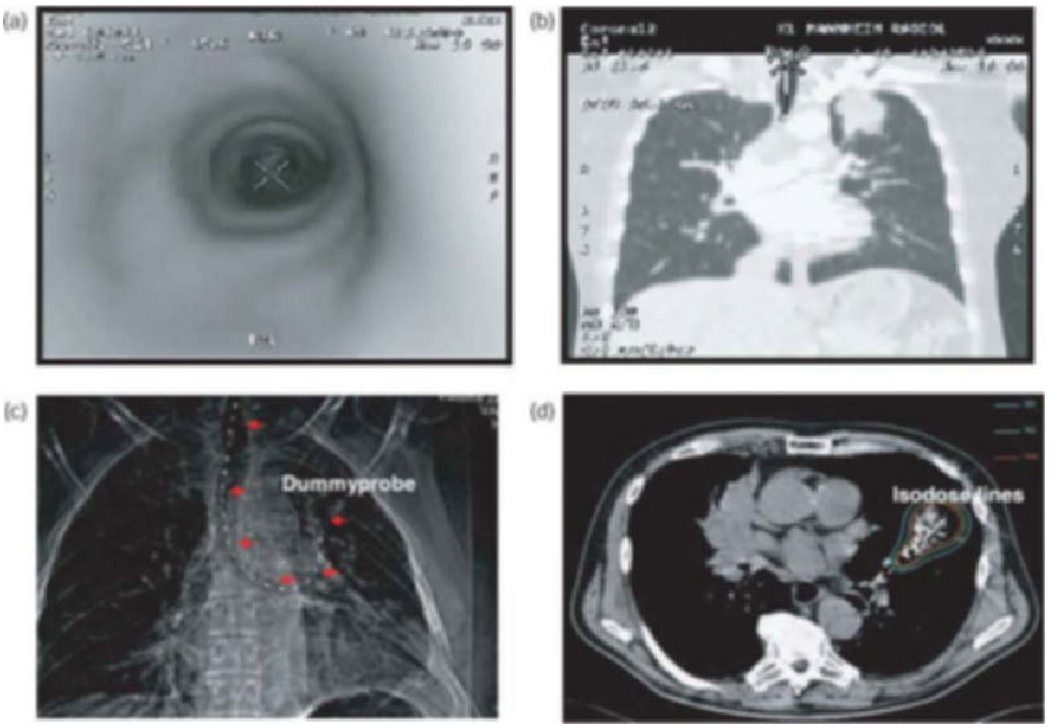

Figure 6.17 Brachytherapy of an inoperable peripheral tumor. By electromagnetic navigation on virtual bronchoscopy (a). (b) A catheter is placed via the viberscope inside the peripheral lesion and a dummy probe is inserted (c) for exact calculation of the dosimetry by distribution of the isodoses lines (d). The bronchovascular bundle can be irradiated simultaneously.

be self-organizing micromachines, exactly adapting themselves to the task for which they have been designed. Functioning in a manner similar to Deoxyribonucleic acid (DNA) replicating itself, they will reorganize and replicate themselves on demand. In addition these molecular machines will also be the transistors of the next chip generation for new computers and lasers. They will be incredibly fast and small and, moreover, their components will be easily degradable [65–69].

Biotechnology has been applied in treatment of lung cancer by injecting wild type p53 integrated in viral vectors. Local application of DNS destructing enzymes might help prevent development of biofilms in stents and grafts. Seeding grafts for replacement of skin, cartilage and other organs is on the horizon. Customized computer-designed biological scaffolds will serve for replacement of damaged structures such as mucosa and cartilages and thus post-intubation stenoses or malacias and other defects will be treated by bioprostheses cultivated from the individual patient's own stem cells. The first experimental procedures are currently being performed by a French group using aortic grafts as scaffold that is temporarily supported by endoluminal stenting.

Documentation

In the face of growing transparency, quality management and communication within the medical community, but also with administration and science, thorough onsite documentation of all pre-procedure patient data, including history, laboratory and functional findings, X-ray and other imaging as well as data of the procedure itself, including still photo slides and video documentation, monitoring of vital functions during the procedure and the recovery period are the essentials for quality management and serve a variety of functions: communication with other health care professionals, longitudinal follow-up of previous

findings and basis for billing. Especially in the context of research, strict data collection is essential. Last and not least, the documentation is a permanent part of the patient's record and may serve legal functions. For example, digital documentation of the cleaning process of the endoscopes (Endoscan®, Olympus Co., Tokyo, Japan) can be helpful in avoiding false litigations in case of infections not attributable to the instruments. Like in other applications continuous digital storage of data comparing the results with general standards serves quality management. Analogous to self-learning oncology programs the quality of the endoscopy department can be continuously monitored and measures for improvement can be taken immediately. Keeping track of medications, devices, time frames, personnel attendance, maintenance schedules, etc. by continuous computer documentation is a great tool in economical structuring and running an endoscopy unit and can save a considerable amount of money by scheduling supply and staff on demand and avoiding unnecessary space and expenses for stock. Integration into the hospital network provides controlled access to data for the physician in charge without the necessity for transferring hard copies of findings from institution to institution. Continuous communication with the supply and financial departments is essential in staying cost-effective and spending resources in the most efficient way [70–73].

Those data are part of an electronic health record (EHR). Currently the standard of health level seven (http://www.hl7.org) is under development for the purpose of achieving the dual goals of controlling healthcare costs and improving patient outcomes by providing standards for exchange, integration, sharing and retrieval of electronic health information with reference to ISO (International Standards Organizations) communications model (http://www.nscee.edu) [74,75].

Communication

Multifunctional image observation

In order to facilitate communication between the staff involved, bronchoscopist, assistant physician, assistant nurses, anesthetist and anesthetist nurse in our institution, procedures can be observed on three parallel monitors that are mounted from the ceiling and can be seen from all working positions. Thus simultaneous control of endoscopic image, fluoroscopy and EBUS image is possible. This allows competent teamwork as all persons can follow the procedure and can react to diagnostic and therapeutic demands in advance and perticularly in an emergency communication and intervention is extremely smooth.

Connection between sources

Online tracking of endoscopes and instruments requires extremely high-powered computers that will be available in the near future. These computers will support the physician's hands as man–machine interfaces. Advanced systems will perform the procedures by steering true robots according to preset programming under the physician's supervision. System integration will be essential for connection, transformation of images according to MPEG (motion picture expert group) standards, storage on video servers and steering of complex video networks.

Room to room

In dedicated multifunctional interdisciplinary endoscopy services online communication room to room is essential. Combined voice and video connection enables simultaneous image analysis by several endoscopists performing parallel procedures for consultation and on site decision making without the necessity to leave one's room. Connection with larger rooms or conference halls allows simultaneous observation by larger groups for teaching and training. Integration of image in image and voice serves interactive communication. In our unit all imaging devices in each suite are connected to a central documentation unit. The selection can be activated by remote control from touch panels. The audio-visual room-to-room communication is implemented into this system. A central communication unit, run by a computer specialist, serves the communication with the other departments of the hospital, the lecture hall and other institutions that can be connected by three integrated double ISDN (integrated services digital network) lines which allow online, interactive communication in real time.

Intrainstitutional

Via intranets department-to-department communication is provided. This applies to stored data such as laboratory findings, radiological and other images and other data. Especially with regard to time and resource saving online communication can be helpful. Thus in a feasibility study we explored whether communication by telepathology might be useful. For that purpose a Leitz tele-microscope that could be steered by the pathologist several buildings away was installed in the endoscopy suite. After quick staining the pathologist could examine cytology specimens while the procedure was still in progress. Within 5–7 mins the results were available, which in almost all cases were diagnostic (Figure 6.18). Thus telepathology enables the saving of money and manpower [76].

Interinstitutional

In times of restricted resources, modern communication systems provide the basis for widespread and evenly distributed patient care on an optimal level. For this purpose, hospitals can be connected through ISDN lines. In future, they will communicate in a high-speed network for communication. This teleconsulting will reduce the need to send patients to distant specialists for consultation ("patient tourism"). The overall results will be an increase in the quality of patient care and reduction of costs [77–82].

Teaching and training

Already, new communication technologies are used for teaching. This education can be performed on an individual basis on single monitors or on a larger scale. For enhancement of interactive communication we currently apply an electronic projecting screen (Smartboard®) that is connected to a computer. By adjusting the digital board according to the projection image the board is activated. Thus virtual pencil notes and drawings can be performed on the image for explanation of complex images. The resulting image can be simultaneously downloaded directly on the computer. This is also possible via long distance, if a partner has the necessary equipment. As an increasing number of images are exchanged via e-mail for discussion, connection of a Smartboard on both sides greatly improves communication.

Training for diagnostic procedures can be performed on mannequins that simulate all procedures by virtual imaging. Procedures can be trained by integration of force-feedback systems, providing a "real touch" feeling and transferring the movements of the bronchoscopist's hand by transformation of its motions into electrical signals. In prospective studies the superiority of a virtual trainer (Immersion®) as compared to conventional training has been demonstrated (Figure 6.19). In future virtual scenarios can be provided for imitation of interventions such as laser surgery, stenting or PDT. Complications can be simulated for training of troubleshooting [83–87].

Figure 6.18 Telepathology. A telemicroscope (Leitz, Wetzlar, Germany) can be maneuvered by the pathologist on long distance communication. The diagnosis can be followed on microscopic image from the monitor and audiovisual communication with the pathologist is provided.

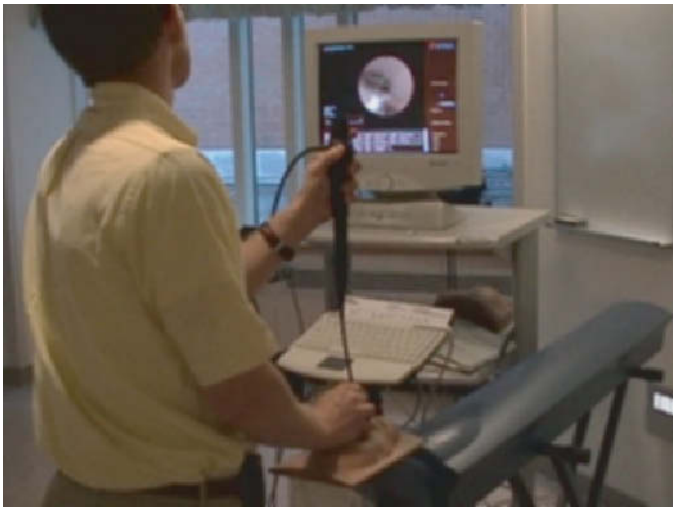

Figure 6.19 Virtual bronchoscopy trainer (Immersion™). The instrument is introduced via a mannequin's face and the simulator provides images of the normal and pathological bronchial anatomy. Additional features such as biopsy and transbronchial needle respiration can be performed in real-time simulation.

For teaching new technologies, groups can be installed on the Internet, also reducing expenses for travel and accommodation of participants. Telecommunication will also enhance new research strategies by evolution of self-organizing research teams that, without guidance by conventional hierarchy, find together in floating teams of varying "chaotic" constellations and goals. This kind of teamwork might prove to be superior compared to current systems in generating new ideas and providing rapid results of research work because they are much more flexible and independent.

Telemedicine and bronchoscopy

Telehealth is the application of electronic information and communication technology to provide and support health care where distance separates the partners (Figure 6.20). It started with the ISDN lines for transmission of sound, video and biometric data. In the era of the Internet, these capacities have widened into a global communication environment. Currently the NGI (next generation Internet/Internet2) is in development, providing 100–1000-fold bandwidth for large data transfer in horizontally and vertically connected "communities." It is expected that improved communication allows reduction in patient and physician traveling by remote conciliary expertise, by which it provides support in decision making and Continuing medical education (CME). In this context legal data protection is an important issue and cost reduction can be expected only after considerable investment in hardware. Telemedicine is already implemented among others in radiology and pathology using the DICOM format (digital communications in medicine) for image transfer. The most advanced development has been made in tele-emergency medicine for the military. Standards are currently developed in various scientific societies, e.g. by the e-health steering committee of the ACCP networks. Liaisons exist to major institutions that have specialized in developing technologies and standards for data processing and communication such as the NSCEE (National Supercomputing Center for Energy and the Environment).

The application potentials are teleinformation, telediagnosis, teleconsulting, telehealthcare, teleconferences and telecourses, telecommunication in research, telepublishing and finally teleintervention. *Teleinformation* can be exchanged not only within the medical community but also with the general population, including information on bronchoscopy, e.g. at www.chestnet.org/education/patient/guides/ bronchoscopy. Nowadays patients are exchanging their experiences while undergoing bronchoscopy and even their reports. For *telediagnosis* textbooks already exist and we have personal experiences in telepathology of TBNA specimens that proved

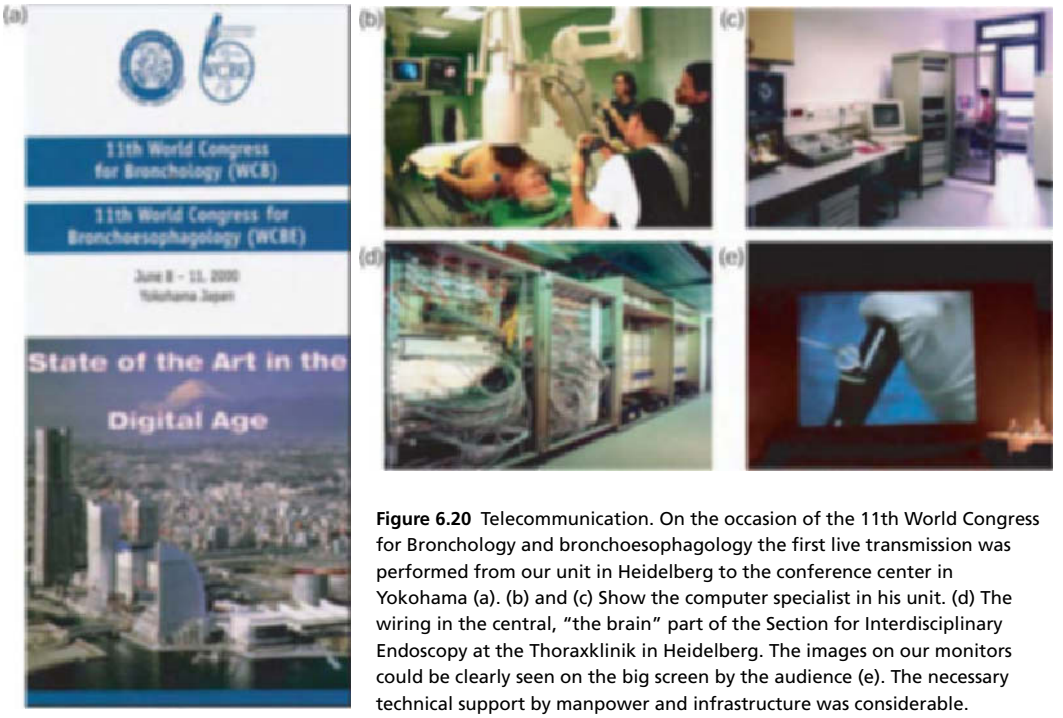

Figure 6.20 Telecommunication. On the occasion of the 11th World Congress for Bronchology and bronchoesophagology the first live transmission was performed from our unit in Heidelberg to the conference center in Yokohama (a). (b) and (c) Show the computer specialist in his unit. (d) The wiring in the central, "the brain" part of the Section for Interdisciplinary Endoscopy at the Thoraxklinik in Heidelberg. The images on our monitors could be clearly seen on the big screen by the audience (e). The necessary technical support by manpower and infrastructure was considerable.

equally reliable as on site pathology. The same is true for *teleconsulting* where we regularly receive and send reports and images for interpretation all over the world. *Teleteaching* can be applied in courses for live demonstrations in local lecture halls, but also for long distance training. The communication technology is so advanced today that live demonstrations have become a regular feature at many international conferences (*teleconferences*) [88,89]. For this purpose streaming and using stable virtual connections via the internet are preferred to transfer via different knots in order to avoid interruption. *Teleresearch* has become available as data can be exchanged at high speed between different institutions via safe lines and even images can be processed for computer analysis via long distance. *Teleintervention* currently is the most demanding technology in telehealth by pushing the limits beyond the bounds of human performance. Today interventional procedures such as bypass surgery can be performed by remote control of instruments from a computer panel. This is possible in one room or room-to-room and with high-speed networks, tele-intervention also becomes possible over long distance, hospital-to-hospital and even continent-to-continent. The first cholecystectomy via long distance was performed in 1987 in Boston by virtual presence of the surgeon in Lyon, France. Interventional procedures require extremely fast and stable communication lines. Of course a skilled bronchoscopist has to be on site for intervention if the connection is interrupted or complications arise (Figure 6.21). In addition malfunction of instruments and computers can be analyzed and repaired by long distance inspection. The communication technology is provided by the Abilene network providing a communication speed of 10 Gigabit/sec on a national backbone for high performance connectivity to support such applications as internet based HDTV (high definition TV) and remote control of distant telescopes. The technology is carried to the extreme when long distance intervention in space missions is concerned. As on spaceflight it happened that a crew member aspirated food, astronauts are trained in intubation so that a bronchoscopist can manipulate

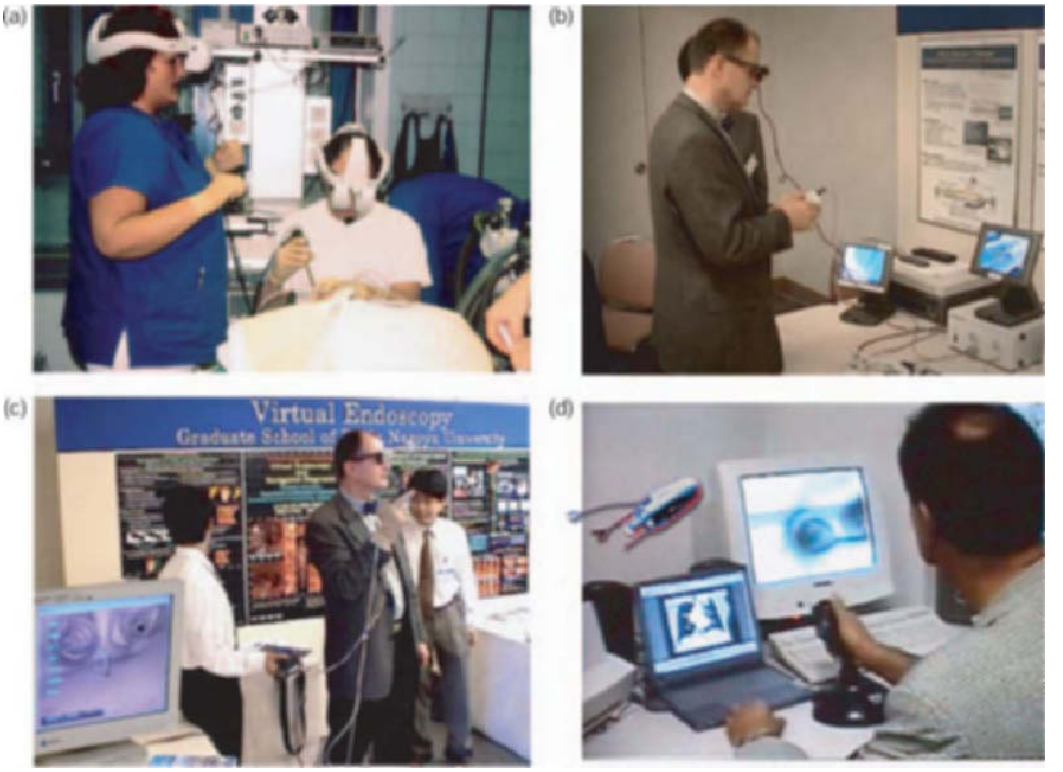

Figure 6.21 May be in the not so far future some of my former visions might become true: image fusion and navigation on head mounted devices (a), steering of probes inside the airways by remote control (b), navigation by cyber spectacles (c) and finally navigation and intervention via long distance by joy stick on computer consoles (d).

bronchoscopes for extraction of the foreign material via remote control [90]. Surgery in space was also the topic of the keynote address by Bernard A. Harris, M.D. at CHEST 2003 in Orlando.

Perspective

Hardly any other technology has influenced the progress of bronchology as profoundly as the computer. As described, computers today are already an integral part of all techniques and will take over conventional technologies with increasing speed, not in a linear but in an exponential way. Thus it is hard to imagine what the field of bronchoscopy will be like 10 years from now. This is especially true given the newly emerging DNA and quantum computer technologies and instruments on a molecular and even atomic basis, the nanotechnology. These ultra small devices with self-reproducing and self-organizing features will revolutionize diagnostic and therapeutic procedures in an unprecedented fashion. In this regard my former statement still holds true: there has always been a broader acceptance for developments in "pure" technology as it is felt that these will improve general health care and life expectancy. With a completely new quality of instruments this is beginning to change considerably. In fact the debate on the necessity of new technologies like robotic and nanotechnology has recently gained worldwide attention and momentum and is currently being documented in the important international journals. As these instruments will be self-controlling and self-repairing and even identically replicating especially in connection with gene technology there is the fear that they might gain uncontrolled artificial life of their own and eventually even endanger mankind and life on earth. On the other hand, we will have no choice but to apply these technologies for the survival of mankind. The "National

Nanotechnology Initiative – Leading to the next industrial revolution" was the top scientific priority issue of the White House for 2001 and the budget for development of these technologies has been doubled. "My budget supports a major new National Nanotechnology Initiative, worth $500 million . . . Imagine the possibilities: materials with ten times the strength of steel and only a small fraction of the weight . . . detecting cancerous tumors when they are only few cells in size. Some of our goals may take 20 or more years to achieve, but that is precisely why there is an important role for the federal government" (W.J. Clinton) [91]. We, as the specialists, who are directly confronted, even involved in these evolutions will not be able to avoid this confrontation but will have to take position on the basis of a rational analysis. In my opinion direct contact between patient and physician will not be replaced by future technology but computers and related technologies will improve our work. "Generally speaking the basic issue for the future is the ideological question of how far mankind decides to propagate the technological acquisition of nature, which has been the recipe for the ascent of mankind from the Savannah of Africa to master and former of the biosphere" [92].

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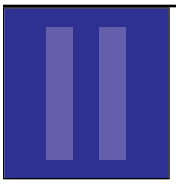

PART II

Advances in therapeutic bronchology

7

CHAPTER 7

Rigid bronchoscopy

Jed A. Gorden, MD *& Douglas E. Wood,* MD

Bronchoscopy, strictly speaking, is a procedure using a tube that serves as a speculum for the examination of the interior of the bronchi.… It was discovered that the bronchi not only expand and contract in inspiration and expiration, respectively; but they elongate and shorten; they bend, twist and are dinged in. The marvelous resiliency of the tracheal bronchial tree was for the first time demonstrated. The endobronchial view was and always will be an awe-inspiring sight.

Chevalier Jackson, "Bronchoscopy: Past, Present and Future"

The purpose of this chapter is to familiarize the reader with the art of rigid bronchoscopy, its versatility and many applications. More and more technology is being adapted to the flexible bronchoscope and tools that were once only available to the rigid bronchoscopist have now been modified to fit the working channel of the flexible instrument. Zavala in an editorial published in Chest in 1974 articulated a forceful position on competing technology, "selection should not be a question of one method *against* the other but of a solid knowledge of the uses and limitations of each instrument" [1]. In order to provide optimal patient care the interventional bronchoscopist of the twenty-first century needs to be facile in both the technology first conceived in the nineteenth century and that introduced in the twentieth century.

Introduction and history

The bronchoscope and the field of bronchoscopy find their roots in the late nineteenth century. The earliest glimpses of the airways were made through the laryngoscope designed by Kirstein which afforded a view through the larynx to the airways below. Later, esophagoscopes, the likes of those designed by Mikulicz and Rosenhiem, were used by pioneers in bronchoscopy like Gustav Killian and Chevalier Jackson to trespass into the airways. Gustav Killian, a German otolaryngologist, is credited with being the "father of bronchoscopy," and was the first to adapt the esophagoscope to the airways. In March of 1897 Professor Killian was presented with a 63-year-old farmer with profound dyspnea, cough and hemoptysis. Killian employing the Kirstein laryngoscope identified an object in the right main stem bronchus. Using cocaine anesthesia and the Mikulicz–Rosenhiem esophagoscope, Killian deployed graspers through the lumen of the scope to secure what turned out to be a pork bone fragment. The 8 mm diameter of the esophagoscope forced the en-mass removal of the object and the scope, and thus the first documented bronchoscopic procedure was performed for a foreign body extraction [2].

Another pioneer and early innovator in the field of bronchoscopy was the American Chevalier Jackson. In accepting the Henry Jacob Bigelow Medal from the Boston surgical society in October of 1928 Jackson defined bronchoscopy as a "procedure using a tube that serves as a speculum for the examination of the interior of the bronchi Bronchoscopy is looking into the living lungs" [3]. Chevalier Jackson would become known as the father of American bronchoscopy. Jackson was trained in laryngology and started his career in endoscopy performing esophagoscopy. He is

credited with engineering a new breed of bronchoscope, a device very similar to the one in current use, as well as instruments for grasping and biopsying tissue. He was a vigorous proponent of education and innovation refusing to patent any invention, so as to ensure the widest possible application and implementation of technology [4].

Bronchoscopy rapidly became ingrained in the culture and practice of pulmonary medicine as a research, diagnostic and therapeutic tool. So common had it become that Jackson quipped to the Boston surgical society, "so many patients have come to the bronchoscopic clinic with conditions having a superficial symptomatic similarity to asthma that we have an aphorism: All is not asthma that wheezes" [3].

With the invention of the flexible bronchoscope in the late 1960s by Professor Ikeda of Japan the number of rigid bronchoscopies performed has fallen off. In a large academic interventional pulmonary program rigid bronchoscopy made up 22% of the total number of bronchoscopies performed in 2003 (Figure 7.1). This figure represents a higher than average use of rigid bronchoscopy than would be found in most programs. Despite rigid bronchoscopy waning in its popularity and even in its availability, it remains an invaluable tool. As interventional bronchoscopists continue to tackle complex airway problems the rigid bronchoscope remains an indispensable tool for the management of central airway pathology.

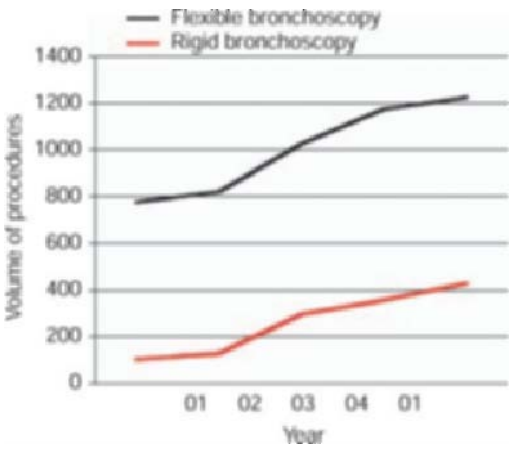

Figure 7.1 Number of rigid and flexible bronchoscopies performed annually for the years 2001–2005 at a large academic interventional pulmonary center.
Source: Personal correspondence.

Central airway anatomy

This section outlines the basic anatomy of the proximal tracheobronchial tree, including lengths and diameters (Figure 7.2). This serves as a reference for the basic dimensions of the standard rigid bronchoscope outlined in the equipment section of this chapter. In addition a critical understanding of airway anatomy is vital to the planning of any airway procedure.

Trachea

The origin of the trachea is defined as the inferior aspect of the cricoid cartilage at the approximate level of the sixth or seventh cervical vertebra. The distal margin of the trachea is the main carina marking the bifurcation of the right and left main stem bronchi at the approximate level of the fifth thoracic vertebra. The trachea is divided into the extra-thoracic trachea which lies above the suprasternal notch, approximately one-third of its total length, and the intra-thoracic trachea which falls below the suprasternal notch making up two-thirds of its total length. The length of the normal adult trachea is 10–14 cm. Computed tomography (CT) guided measurements of the intra-thoracic tracheal length range from 6–9 cm in adults. The coronal diameter of the normal trachea in adult males range from 1.3 to 2.5 cm; the sagital diameter ranges from 1.3 to 2.7cm. The coronal diameter of the normal trachea in women ranges from 1 to 2.1 cm, the sagital diameter 1 to 2.3 cm [5–7]. The length of the pediatric trachea is the same for males and females representing gender similar growth rates from birth to adulthood. At age 14 the female trachea ceases to grow while the male trachea continues to enlarge but not lengthen until maximum adult diameter is achieved [8]. The trachea maintains its structure with the rigid structural support of 18–24 C-shaped cartilaginous anterior rings. The posterior wall of the trachea is a membranous band and lacks cartilaginous support. The diameter of the intra-thoracic trachea is dynamic

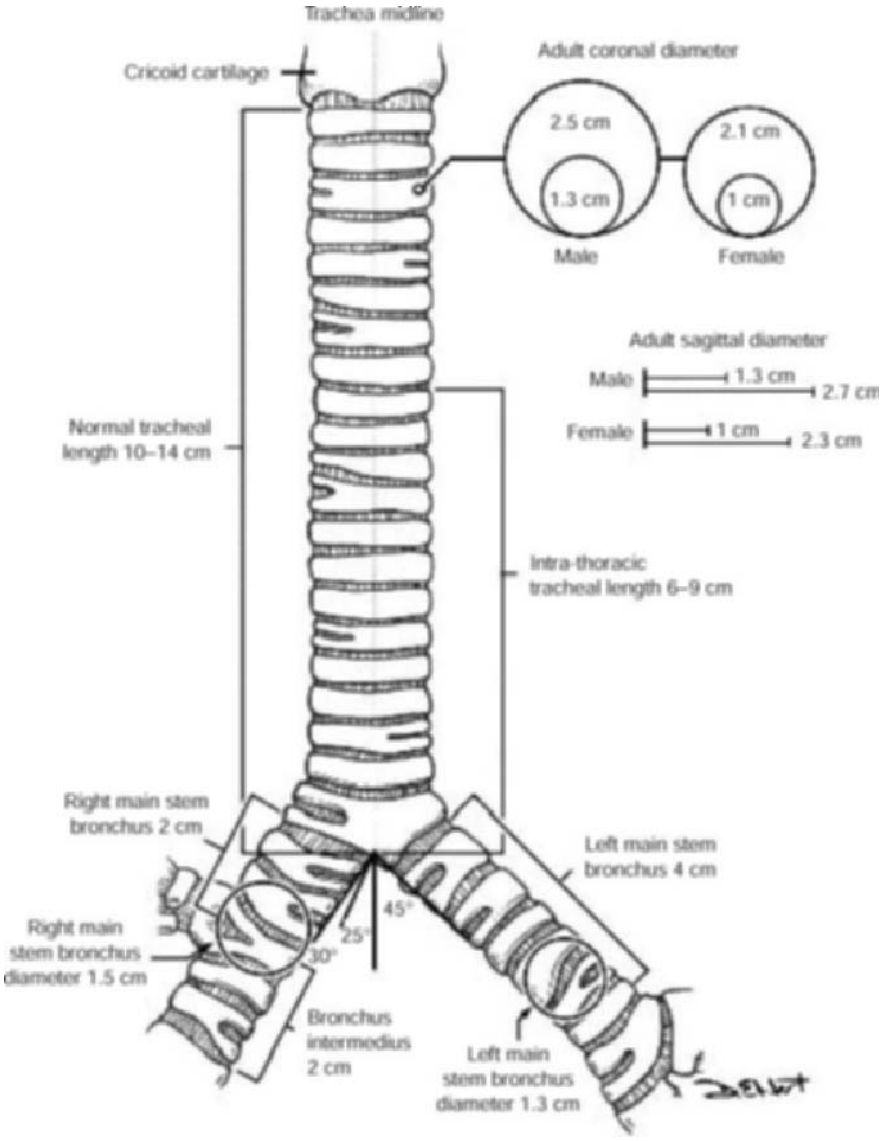

Figure 7.2 Anatomy of the proximal tracheobronchial tree.

and expands with inspiration and recoils upon expiration [5–7].

Main carina

The main carina marks the bifurcation of the trachea into the right and left main stem bronchi. Anatomically this relates to the manubriosternal junction or the fifth–sixth thoracic vertebrae. There is wide variability in the accepted normal subcarinal angle with mean angles ranging from 56–61° [5]. In adults the left main stem bronchus branches at a more obtuse angle relative to the midline trachea in contrast to the right main stem bronchus. In the pediatric population ages birth to 15 years, there is no statistical difference in the right and left main stem bronchial angles when measured from the midline trachea [9].

Right main stem bronchus

The right main stem bronchus is defined at its proximal end by the main stem carina and at its distal

end by the right upper lobe orifice. In adults the course of the right main stem bronchus off the trachea is more direct than that of the left main stem bronchus. The right main stem bronchus diverges off the trachea at an angle of 25–30° from the midline. The approximate diameter of the right main stem bronchus is 1.5 cm. The approximate length of the right main stem bronchus is 2 cm [5,6].

Bronchus intermedius

The bronchus intermedius is the continuation of the right bronchus distal to the right upper lobe take off. The proximal border is the right upper lobe bronchus and the distal border is the right middle lobe and right lower lobe bifurcation. The length of the bronchus intermedius is approximately 2 cm [5].

Left main stem bronchus

In adults the left main stem bronchus forms a more obtuse angle of divergence from the midline trachea than the right main stem. The left main stem bronchus diverges from the midline trachea at an approximately 45° angle. The diameter of the left main stem is approximately 1.3 cm and the length is approximately 4 cm. The left main stem bronchus is considered the lumen from the proximal main carina on the left to the branching of the left upper and lower lobes [5].

Equipment and specifications

The rigid bronchoscope is a powerful yet simple piece of equipment. The components of the rigid bronchoscope include (Figure 7.3): the barrel, light source, multifunction head, telescopic lens and fenestrated cap. The rigid bronchoscope can accommodate a multitude of graspers, dilators, biopsy forceps, stent delivery devices, catheters and suction devices.

The bronchoscope barrel is a hollow metallic tube with a beveled distal tip with distal side ventilation ports. At its proximal end there are adapters for the light source and the multifunction head. Rigid bronchoscopes come in various lengths ranging from 33 to 43 cm depending on type and manufacturer. The inner diameter of the adult rigid bronchoscope ranges from approximately 7 to 13 mm and the outer diameter ranges from 11 to 14 mm depending on the specific scope and manufacturer.

The optional multifunction head has multiple ports to accommodate ventilation and procedural instruments or suction simultaneously. The ventilation port is attached to the ventilator or ambu bag circuit for the purposes of assisting respiration. Because the rigid bronchoscope is uncuffed a significant air leak may occur and tidal volumes delivered will not reflect alveolar tidal volume. These issues are frequently circumvented by using jet ventilation for endoscopic procedures.

Accessories have been designed to pass through the main working lumen or barrel of the bronchoscope. Principal accessories include (Figure 7.4): suction catheters, graspers, biopsy forceps, dilators and stents. To visualize the airways the bronchoscopist can: directly sight through the lumen of the scope, deploy a telescopic camera, pass a flexible bronchoscope or employ optical forceps which combine the telescopic camera and specialized graspers (Figure 7.5).

Our practice routinely employs both rigid and flexible bronchoscopy together in all procedures. The patient is intubated with the rigid bronchoscope and the telescope and camera are used to assist in airway inspection and procedural planning. The flexible bronchoscope can also be inserted to extend the endoscopy into the lobar and segmental levels, to inspect the airway beyond obstructing lesions or areas of bronchial distortion, and to simplify simultaneous suction and viewing when the airway is obscured by blood or secretions.

Indications

Bronchoscopy serves two main purposes; diagnostic data collection and therapeutic intervention. Early bronchoscopists were generalists required to manage a range of insults from foreign body aspirations to esophageal strictures due to caustic lye ingestions. The lung cancer epidemic of the mid twentieth century broadened the need for safe tissue diagnosis as well as therapeutic interventions from the bronchoscopist. Since the introduction of the flexible bronchoscope the primary role of the rigid bronchoscope

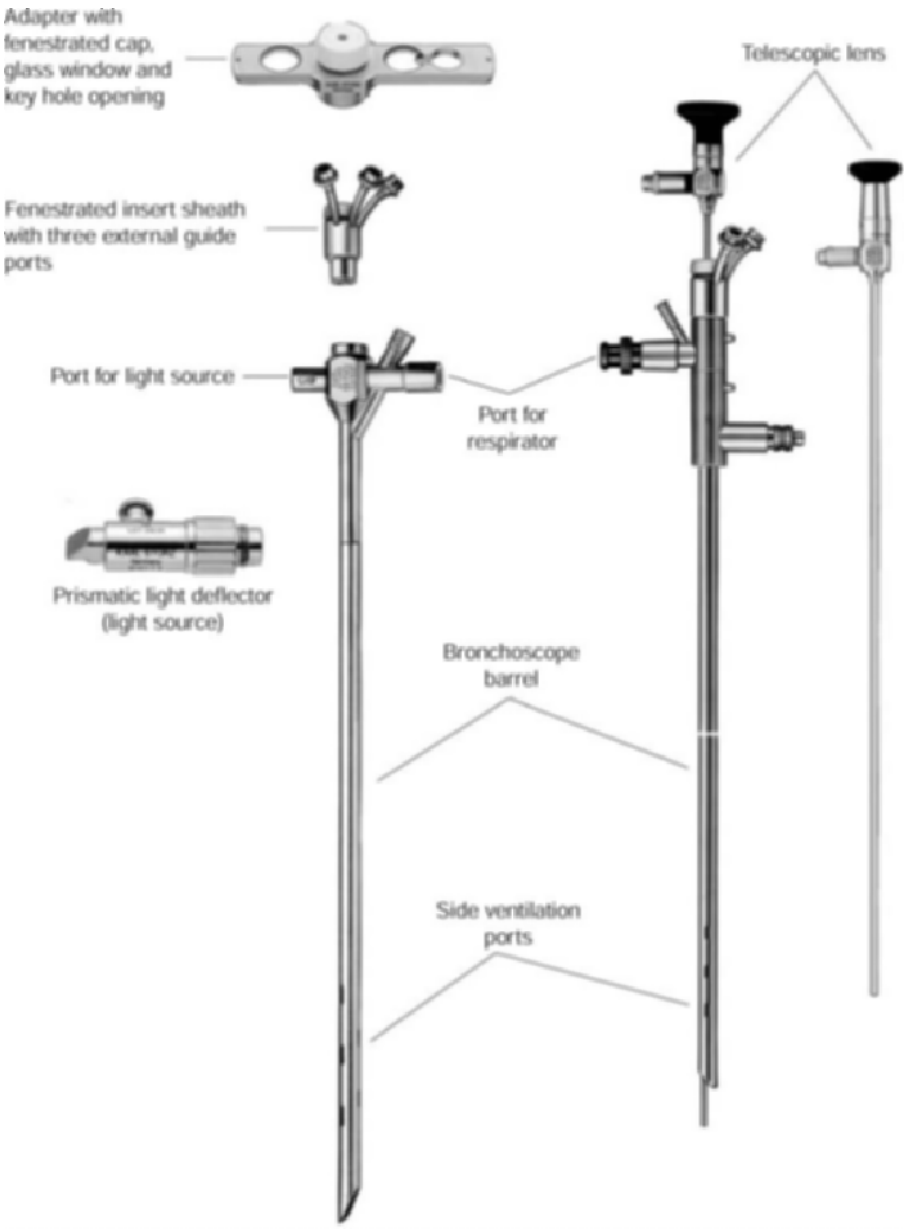

Figure 7.3 The primary components of the rigid bronchoscope. (Reproduced with permission from Karl Storz Endoscopy, America, Inc.)

has been in the therapeutic management of airways pathology. The principal indications for rigid bronchoscopy include: large tissue biopsies, removal of complex foreign bodies, management of massive hemoptysis, and therapeutic interventions for intrinsic airway obstruction and extrinsic airway compression (Table 7.1).

There are numerous specific technical advantages to the rigid bronchoscope in comparison to the flexible bronchoscope that need to be emphasized (Table 7.2). It is important to remember that the flexible bronchoscope complements the rigid bronchoscope and should not replace it in the armamentarium of the chest physician.

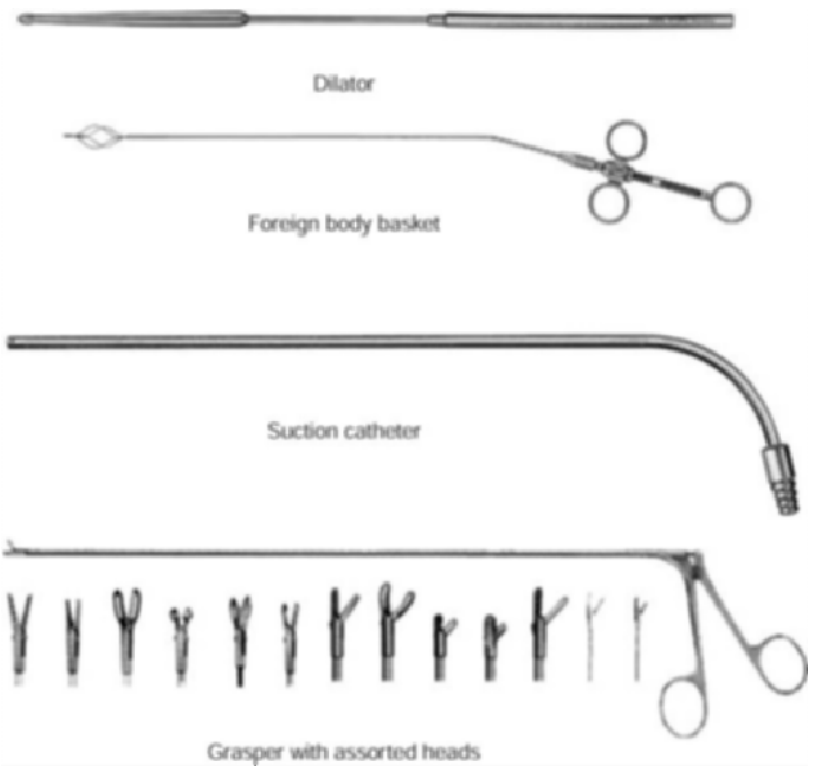

Figure 7.4 Assortment of accessories designed to pass through the barrel of the rigid bronchoscope. (Reproduced with permission from Karl Storz Endoscopy, America, Inc.)

Figure 7.5 Optical forceps designed to pass through the barrel of the rigid bronchoscope. (a) Optical forceps with assorted heads. (b) Optical forceps seen grasping a peanut. (Reproduced with permission from Karl Storz Endoscopy, America, Inc.)

Table 7.1 Indications for rigid bronchoscopy.

Large volume tissue biopsies
Management of massive hemoptysis
Foreign body extraction
Direct management of endobronchial obstruction
Mechanical coring of lesion using beveled tip
Direct dilation of airway lumen
Indirect management of endobronchial obstruction
Nd–YAG laser
Cryo therapy
Electrocautery
Bougie dilation
Microdebrider
Management of extrinsic airway lumen compression
Silicone stent
Expandable stent

Table 7.2 Advantages of the rigid bronchoscope.

Large lumen accommodates variety of larger tools and devices
Large suction capability
Ventilating lumen minimizes airway obstruction
Ability to deploy solid and expandable stents
Direct ability to manipulate lesions and achieve hemostasis
Decreased risk of airway fire when using laser
Direct airway control
Well-supported oxygenation and ventilation throughout procedure
Allows for prolonged procedures

Foreign body extraction

> How many people have perished, perhaps in an instant and in the midst of a hearty laugh, the recital of an amusing anecdote, or the utterance of a funny joke, from the interception at the glottis of a piece of meat, a crumb of bread, a morsel of cheese, or a bit of potato without a suspicion, on the part of those around, of the real nature of the case! Many a coroner's inquest has been held upon the bodies of the victims of such accidents, and a verdict rendered that they died by the visitation of God, when the actual cause of death lay quietly and unobserved at the door of the windpipe of the deceased.
>
> Samuel D. Gross in L. F. Clerf, "Historical Aspects of Foreign Bodies in the Air and Food Passages"

There is no prospective randomized literature comparing rigid bronchoscopy to flexible bronchoscopy for foreign body extraction from the airway. Although bronchoscopy has no effect on the acute event of foreign body aspiration, it is clear that the advent of bronchoscopy has positively impacted the subacute and chronic sequelae associated with airway foreign bodies. These are namely: respiratory distress, obstructive pneumonia, and lung abscess. Jackson reported in 1936 that the mortality associated with foreign body aspiration dropped from 24 to 2% with a 98% success rate of foreign body extraction using his bronchoscope and graspers [10]. The nature of aspirated foreign bodies has certain geographic and cultural variability. The most cited foreign body aspirations are vegetable matter, peanuts or bones [11–18]. The most common age groups for foreign body aspiration are children under the age of three [11,15] and adults in the sixth and seventh decades of life [17]. The predominance of aspirated foreign bodies occurs in children. The most common anatomic site for foreign body lodgment in adults is the right bronchial tree.

The rigid bronchoscope has been supplanted by flexible bronchoscopy in many respects but there remains a significant role for rigid bronchoscopy in foreign body removal. In the Mayo clinic case series published in 1990 involving 60 foreign bodies, rigid bronchoscopy was successful in 43 of 44 adult patients (98%), including 6 out of 7 instances where flexible bronchoscopy failed to retrieve the foreign body. In comparison flexible bronchoscopy was successful in 14 of 23 patients (60%) [17]. It is reasonable to initially attempt foreign body extraction with the flexible bronchoscope, with a high likelihood of success, but rigid bronchoscopy is a useful adjunct and prompt conversion to rigid bronchoscopy may save the patient from multiple interventions, obstructive complications or even the need for surgical intervention. Each of the two technologies for foreign body extraction has merit and the bronchoscopist of the twenty-first century must be facile in both to determine the most appropriate tool for the clinical scenario at hand.

The advantage of the rigid bronchoscope is the diameter of the working channel and the larger scale of the working instruments. This gives the bronchoscopist the ability to manage foreign bodies

of different size, shape and surface texture. The large scale of the working instruments allows for greater ease of grasping all or fragments of the foreign body and more rapid removal. It is critical to understand that the luminal diameter of the rigid bronchoscope and the flexible bronchoscope do not dictate the size of the foreign body which can be removed. The luminal diameter of the scope dictates only the size of the working instrument which will grasp and manipulate the foreign body. The foreign body, the grasper and the scope (both rigid and flexible) can be removed en-mass if necessary to recover the foreign body. A number of specialized graspers are made to deploy through the rigid bronchoscope. Endoscopic magnets can be deployed through the working channel of the rigid bronchoscope to retrieve magnetic and ferromagnetic foreign bodies [19].

Pediatric foreign body removal

Foreign bodies in pediatric patients can be found in all segments of the lung and do not always display the right-sided dominance seen in adults [13,20,21]. Aspiration location may be related to anatomical size of the airway. Possibly more important than the narrow nature of pediatric airway is difference in carinal angle between children and adults. Children up to the age of 15 years have equal right and left bronchial angles [9].

Rigid bronchoscopy is the instrument of choice for removal of foreign bodies in children below age 10–13, due to the tracheal luminal diameter. The ventilating pediatric rigid bronchoscope offers the greatest airway control and greatest instrument maneuverability allowing for the rapid removal of airway foreign bodies. Anesthesiologists should minimize forceful positive pressure ventilation and preferentially allow spontaneous respiration when possible to minimize the potential risk of dislodging the foreign body and forcing it distally.

Hemoptysis

Although no prospective randomized data has compared rigid and flexible bronchoscopy in the management of massive hemoptysis, there is little disagreement regarding the value of rigid bronchoscopy in salvaging a threatened airway and providing the quickest and most reliable localization of bleeding and temporary airway control.

The goals in managing massive hemoptysis are securing the airway, identification of the bleeding source, isolation of the bleeding area to prevent soiling of the unaffected lung and cessation of bleeding. In the absence of empiric data supporting a singularly superior bronchoscopic technique, a thorough knowledge of the strengths and weakness of the rigid and the flexible bronchoscope is required of the twenty-first century bronchoscopist.

Localization of nonlife threatening hemoptysis is best done employing the flexible bronchoscope. It is rapidly available, does not require general anesthesia, can be performed at the bedside and allows for the most thorough airway survey. This rapid diagnostic survey helps with therapeutic planning. Diagnostic bronchoscopy should be done early, within 24 h of bleeding to maximize the chances of localizing [22–24] or, at a minimum, lateralizing the bleeding source. The primary limitations of flexible bronchoscopy are diminished visibility even in the presence of small volumes of blood and low suction capability. In the presence of active bleeding, it may be very difficult for the flexible bronchoscope to adequately obtain and maintain a clear airway, limiting both the goal of airway control, and the goal of bleeding localization.

Rigid bronchoscopy affords the operator the greatest array of therapeutic tools as well as the greatest suctioning capacity while maintaining a stable airway and optimal visibility. The greatest advantage of rigid bronchoscopy in the setting of massive hemoptysis with respiratory embarrassment is large-bore suctioning. For proximal airway bleeding lesions the rigid bronchoscope itself can be used to provide direct mechanical tamponade or directed placement of a balloon device. The desire to perform a flexible bronchoscopy should not delay transfer to the operating room for a more definitive endoscopic approach [25].

Airway obstruction

When conceptualizing central airway obstruction (trachea, carina, mainstem bronchi and bronchus intermedius) and the appropriate therapeutic intervention, it is best to differentiate lesions

which cause internal luminal obstruction (intrinsic obstruction) from those caused by external luminal compression (extrinsic obstruction), although they may frequently coexist in the same patient.

In cases of symptomatic airway compromise the intervention should be rapid and effective with low associated morbidity and mortality. If performed as a staged procedure to establish a stable airway prior to more definitive surgical management, the endoscopic intervention should not interfere with the ultimate surgical plan. If the intervention is palliative it should require limited follow-up care in an effort to maximize the positive impact on patient quality of life. The rigid bronchoscope alone is an effective tool to relieve intrinsic airway obstruction and satisfies the above goals. Proximal endobronchial lesions can be effectively removed either with biopsy forceps or using the beveled tip of the bronchoscope directly. Suctioning of all secretions should be performed to visualize the obstructing lesion, localize the base and ascertain the extent of obstruction. It is critical to determine the axis of the airway and maintain this spatial orientation during the entire procedure. The obstructing lesion should be instrumented in parallel to the axis of the airway to avoid perforating the airway, inducing pneumothorax or breaching a vascular structure.

To remove the obstructing lesion by blunt dissection (core-out) with the rigid bronchoscope, place the beveled tip of the bronchoscope against the base of the lesion and with a gentle twisting motion, with forward pressure, bluntly dissect the lesion off the airway wall. Fragments can be removed with graspers and suction to prevent airway occlusion. It is critical to inspect airways distally. Often a flexible bronchoscope is passed through the lumen of the rigid scope to inspect distal airways for secretions, clots or obstructing tissue which may have migrated during the procedure. Some operators suggest the prophylactic instillation of epinephrine to induce vasoconstriction and minimize the risk of bleeding at the time of blunt dissection. In our experience and published case series rigid bronchoscopic blunt dissection of obstructing tumors rarely results in severe bleeding [26]. Minor bleeding can be addressed by direct tamponade with the rigid bronchoscope or other direct topical measures. While the risk of severe bleeding is very low the operator must be cautious when approaching highly vascular tumors like arteriovenous malformations and hemangiomas. In our experience vascular tumors like carcinoids and renal cell carcinoma metastases are not contraindications to this method but must be approached with caution and preparation with large-bore suctioning, and possible hemostatic measures like laser or cautery.

Other common modalities for managing internal obstructing lesions focus on the removal of tissue with instruments deployed through the rigid bronchoscope: ND-YAG laser, cryotherapy, electrocautery and microdebrider. Modalities for managing external luminal compression focus on restoring airway conformation with airway stents. Each one of these therapeutic modalities will be discussed in depth elsewhere in this book.

Operating theater

Rigid bronchoscopy is usually performed in the controlled confines of the operating room, but can be performed in an endoscopy unit equipped for general anesthesia. A fully trained staff is essential to the safe performance of the procedure. The team needs to include an anesthesiologist or certified nurse anesthetist. The bronchoscopist must be present before anesthesia is initiated to help insure an adequate secure airway is obtained. This is critical when managing patients with airway obstruction. Although the anesthesiologist is responsible for the airway in most general anesthesia cases, in the setting of central airway compromise, the interventional bronchoscopists and anesthesiologist need to have a coordinated plan for airway control before induction of anesthesia. Additional members of the team include a trained bronchoscopy assistant familiar with all the equipment required for the procedure. The patient should be appropriately monitored with secure IV access, pulse oximetry, blood pressure and heart rate monitoring.

Technique

Proper patient position is critical when intubating the airway with the rigid bronchoscope. A tooth guard is placed to protect the upper teeth during the procedure. The patient is positioned in the supine position with the head in the sniffing position. This maneuver elevates the larynx and creates a

more linear route through the vocal cords. The goal is to achieve anterior linear alignment of the oral, pharyngeal and laryngeal axes in order to access the trachea and mainstem bronchi; the operator needs to determine the optimal way to achieve this for each individual patient (Figure 7.6).

There are two principal techniques of intubating the trachea with the rigid bronchoscope: the direct method and the technique employing a laryngoscope.

In the direct method the patient is positioned as described earlier and the bronchoscope is used directly to intubate the trachea. The median sulcus of the tongue and the uvula define the midline. The bronchoscope is inserted along the median sulcus of the tongue and advanced in the plane perpendicular to the operating table with the beveled edge anterior. The bronchoscope is advanced while either sighting directly down the barrel or through the telescope and camera optics. It is critical to advance the scope under direct observation and insure midline position. The first visualized structure is the uvula as the scope is advanced to the base of the tongue. The tongue base is then used as a fulcrum, the hand supporting the operator end of the scope pulls back from a 90° angle to an approximate 45° angle and the hand supporting the distal end applies gentle anterior pressure. Care is necessary to keep the scope fulcrum on the operator's fingers near the mouth, rather than on the patient's teeth. As the scope is advanced past the base of the tongue the epiglottis comes into view. The scope is passed under the epiglottis, which is lifted directly anterior to expose the vocal cords. A common error is allowing the bronchoscope to pass too far beyond the epiglottis before lifting to expose the vocal cords. This results in the scope lying behind the larynx, and the lifting maneuver exposes the esophagus rather than the glottic opening. With the vocal cords visualized the scope is rotated 90° to the right or left so the bevel is parallel to the cords to minimize vocal cord trauma. Once past the cords, the scope is advanced to the midtrachea to insure the distal lateral ventilation ports are well within the airway and the ventilating system can be attached to establish active ventilation. If there is difficulty identifying the epiglottis a laryngoscope can be used in the left hand to identify the epiglottis and then the bronchoscope is advanced with the right hand as described earlier. When using the rigid bronchoscope in an intubated patient the bronchoscope is advanced adjacent to the endotracheal tube to the level of the vocal cords. The endotracheal tube is then removed and the rigid bronchoscope is advanced through the vocal cords and into the tracheal lumen.

Given the inflexibility of the rigid bronchoscope it can only be directed into the right mainstem bronchus, left mainstem bronchus and bronchus intermedius. To cannulate the right main stem bronchus the patient's head is turned toward the left, creating a straight path to the right mainstem bronchus. To cannulate the left mainstem bronchus the patient's head is turned toward the right, and the scope itself can be used to straighten the slight curve of the bronchus.

Contraindications

There are very few absolute contraindications associated with rigid bronchoscopy. There are anesthetic concerns; patients with contraindications to general anesthesia like unstable coronary syndromes need to undergo a risk assessment to determine whether and when to proceed with the procedure. Other concerns are anatomic; patients who cannot withstand hyperextension of the neck or rotation of the neck due to a fused or unstable cervical spine should not be considered for rigid bronchoscopy. This patient population is best assessed by flexible bronchoscopy while maintaining a stabilized cervical spine. Patients with unstable midline facial fractures should also avoid rigid bronchoscopy.

Teaching and guidelines

Since the introduction of flexible bronchoscopy in 1969 there has been a general decline in the use of the rigid bronchoscope. Physicians less accustomed to rigid bronchoscopy are less apt to consider it in their therapeutic algorithms. Rigid bronchoscopy is not a component of pulmonary training, although it still is taught at some centers with active interventional pulmonary divisions. Although rigid bronchoscopy is now performed primarily by thoracic surgeons, it is becoming less and less a part of U.S. thoracic surgical training except in a handful of

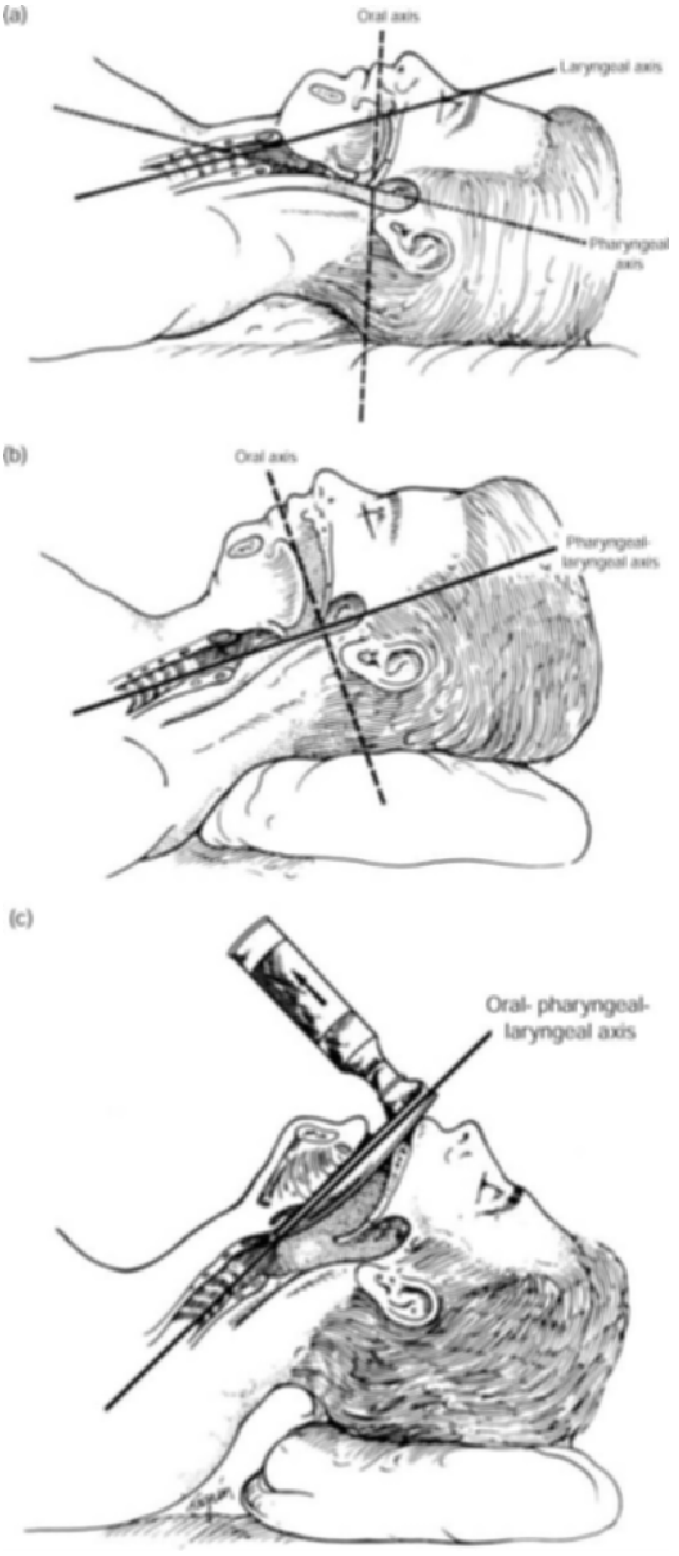

Figure 7.6 Head position and the alignment of the oral, pharyngeal and laryngeal axes. (a) Head in the neutral position. There is no alignment of the oral, pharyngeal or laryngeal axes. (b) Head raised with cervical flexion. This position leads to alignment of the pharyngeal and laryngeal axes. (c) Head elevated with atlanto-occipital extension (the sniffing position). This position results in alignment of all three axes: the oral, pharyngeal and laryngeal axes. (Images reprinted from James T. Roberts. Clinical management of the airway. In: Oral intubation techniques 1994, 159–160, with permission from Elsevier.)

programs with major general thoracic and airway surgery programs. The father of American bronchoscopy, Chevalier Jackson, was a pioneer and champion of the importance of education in procedural practice. Upon being awarded the Henry Jacob Bigelow Medal by the Boston surgical society in 1928, he stated in his acceptance speech, "if an esophagoscope is put into the hypopharynx and simply pushed upon, the one place into which it will not go is the esophagus. . . For this reason the teaching of these procedures becomes one of the most important tasks of postgraduate education."

One teaching modality is surgical simulation, which might employ synthetic models, human cadavers or animal models [27]. An intensive surgical skills course employing a pig model has been shown to decrease errors and surgical time in bronchoscopic foreign body removal [28]. Simulation though is only an adjunctive educational tool that complements but does not render obsolete one-on-one mentoring with hands-on training in actual patients.

In 2002 the European Respiratory Society (ERS) and American Thoracic Society (ATS) published a combined statement on interventional pulmonology, which included recommended training requirements in rigid bronchoscopy [29]. In 2003 the American College of Chest Physicians (ACCP) published its own guidelines on interventional pulmonary procedures which included training recommendations for rigid bronchoscopy [30]. These societies recommend the following three training criteria as a minimum standard of proficiency: (i) extensive experience in flexible bronchoscopy and endotracheal intubation. (ii) At least 20 rigid bronchoscopies should be performed in a supervised setting before attempting the procedure alone. (iii) To maintain proficiency in rigid bronchoscopy it is recommended that the procedure be performed 10–15 times per year.

Conclusion

Rigid bronchoscopy remains an important tool in the arsenal of the interventional bronchoscopist. Even as technology advances the capabilities of the flexible bronchoscope, rigid bronchoscopy has proven to remain an indispensable technique because of the unique advantages it provides. With this simple tool the bronchoscopist can deploy blunt dissection, Nd–YAG laser therapy, cryotherapy, electrocautery or the microdebrider to remove endobronchial obstructing lesions. Using a single tool the operator can remove an endobronchial obstructing lesion and deploy a stent to ensure airway patency.

Rigid bronchoscopy remains an efficient tool for managing such classic problems as foreign body aspiration and massive hemoptysis and it remains the standard of care for managing airway problems in children and infants. The rigid bronchoscope, a simple tool developed in the nineteenth century is proving to still be an invaluable companion to technology that is expanding in the twenty-first century.

Pre-procedure planning is critical to approaching any airway problem. Every airway case requires the thoughtful consideration of all medical, surgical, endobronchial and radiologic options before proceeding.

> In the future, as at present, the internist will tap and look and listen on the outside of the chest, (and it is marvelous what diagnostic information is thus obtained); the roentgenologist will continue to look through the patient; but in continually increasing proportion of cases, the surgeon, the internist and the roentgenologist will ask the bronchoscopist to look inside the patient.
>
> Chevalier Jackson,
> "Bronchoscopy: Past, Present and Future"

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8

CHAPTER 8

Fire and ice: laser bronchoscopy, electrocautery and cryotherapy

Michael A. Jantz, MD *& Gerard A. Silvestri,* MD, MS

Airway obstruction, whether from a benign or malignant process, can be a significant cause of morbidity and may be acutely life threatening. The incidence of airway obstruction is not known. Central airway obstruction most commonly occurs secondary to primary lung cancer although other malignancies may metastasize to the airway. Approximately 75% of patients with lung cancer will have locally advanced or metastatic disease at the time of diagnosis and, thus, will not be candidates for curative resection. It has been estimated that about 30% of patients will develop obstruction of the airways at some point in their disease and that about 30% will die from pulmonary complications such as hypoxemia, hemoptysis or postobstructive pneumonia. As such, given the large number of patients worldwide who develop lung cancer, there is clearly a significant need for treatment options to palliate these symptoms. These options include external beam radiotherapy, chemotherapy and, more recently, bronchoscopic therapies such as laser bronchoscopy, electrocautery, cryotherapy, photodynamic therapy and brachytherapy. In addition to palliating patients with malignant airway obstruction, bronchoscopic therapies also allow for treatment of benign airway tumors and conditions that cause benign tracheobronchial stenosis. In this chapter, we will focus on three of the treatment modalities that have been widely utilized: laser bronchoscopy, electrocautery and cryotherapy. We will review the indications, techniques and outcomes for these procedures.

Laser therapy

The term laser is an acronym for light amplification of stimulated emission of radiation. Laser light is characterized by electromagnetic energy that is collected and delivered as parallel, synchronized rays of light of the same wavelength. At the atomic level, electrons orbit the nucleus of the atom consisting of protons and neutrons. With application of an external source of energy, the electron absorbs energy and moves from an orbit of lower energy to an orbit of higher energy. This condition, referred to as an excited state, is unstable and upon return of the electron to the lower energy state, or resting state, a photon is released. Photons are discrete packets of radiant energy that travel in waves and produce what we refer to as light. To produce the stimulated emission of light, a greater number of electrons must exist in the excited state rather than in the resting state, a condition known as population inversion.

Laser light is created by using an energy source to excite a medium in an optical chamber that contains a fully reflective mirror at one end and a partially reflective mirror at the other. The medium may consist of a solid, liquid or gas material. By applying electrical, thermal or optical energy to the medium, electron excitation occurs with

development of population inversion and emission of photons. The mirrors and walls of the chamber reflect photons back into the medium producing further electron excitation. The laser light leaves the chamber through the partially reflective mirror. Laser light has three unique characteristics that make it useful: monochromaticity, coherence and collimation. Monochromaticity means that the waves of light have the same wavelength and energy. Coherence refers to all waves of light in the beam being in phase in time in space resulting in concentration of energy at the target point. Collimation means that the waves of light travel along parallel ray directions, thus allowing the laser light to travel with minimal scatter and loss of intensity.

Laser light can interact with tissues in different ways. The light energy may be converted into thermal energy producing cutting, vaporization or coagulation of the tissue. In addition, the laser may mechanically disrupt tissues by producing pressure waves or by the vaporization of intracellular and extracellular water. Laser light can also be used in photodynamic therapy to generate biochemical reactions by the interaction of the light energy with photosensitizing substances. At the tissue surface, the light may be reflected, scattered, transmitted or absorbed. Lasers with high absorption and low scattering will produce tissue cutting while those with low absorption and high scattering will provide good coagulation. The amount of tissue destruction produced by the laser is determined by the degree of tissue absorption, power density of the laser beam, distance of the laser tip to the target and duration of laser application to the target [1].

A number of laser systems have been developed and used for medical applications. The various lasers have different characteristics as a function of using different substances as the laser medium. Each substance produces a different wavelength of emitted light. The most commonly used lasers for bronchoscopic applications have been the carbon dioxide (CO_2) laser and the Neodymium:Yttrium–Aluminum–Garnet (Nd:YAG) laser. The CO_2 laser was the first laser to be used in the airways. It generates an invisible infrared beam at a wavelength of 10–600 nm. Because the CO_2 laser beam is not visible, a coaxial helium–neon laser, which produces light in the visible range, is used in conjunction with it as an aiming guide. The CO_2 laser exhibits high absorption and low scatter coefficients with predictable depth of penetration of 0.5–1 mm, thus making it valuable for precise surgical applications [2,3]. The CO_2 laser has been used extensively for malignant lesions of the head and neck, benign subglottic and tracheal stenosis and proximal tracheal tumors as well as uvulopalatopharyngoplasty [4,5]. The CO_2 laser has two properties that have limited its use for bronchoscopic application. First, due to its long wavelength an articulating arm and series of mirrors are required to direct the beam making alignment of the beam down the entire length of the rigid bronchoscope difficult. The wavelength of the CO_2 laser prevents transmission though optic fibers that would allow it to be used with flexible bronchoscopes. Second, the CO_2 laser has excellent cutting properties but poor coagulation properties, which creates problems with bleeding control during tumor resection. As such, the CO_2 laser is used predominantly for otolaryngology applications.

The Nd:YAG laser is most commonly utilized in pulmonary medicine and will be the focus of this section on laser bronchoscopy. The Nd:YAG laser produces an invisible infrared beam at a wavelength of 1064 nm. The beam is delivered via a flexible quartz fiber that can be passed through a rigid or flexible bronchoscope. A helium–neon alignment laser is also used for target localization of the Nd:YAG laser. Power output of the laser can be varied between 5 and 100 W. At lower settings, tissue photocoagulation is the predominant effect while at higher settings tissue vaporization also occurs. The Nd:YAG laser exhibits differences in absorption in lightly colored versus darkly colored tissues. Absorption is low in lightly pigmented tissues and high in darkly pigmented tissues. Coagulation of proteins and blood vessels deep to the surface provides excellent hemostasis. Tissue penetration ranges from 5 to 10 mm and the volume of tissue affected by the laser is greater than that of the CO_2 laser.

Other lasers less commonly have been utilized for pulmonary applications. The potassium-titanyl-phosphate (KTP) laser generates a wavelength of 532 nm. Darker colored tissues highly absorb this wavelength of light but more precise cutting is possible than with the Nd:YAG laser. The KTP laser

has been used for photocoagulation and resection of tracheobronchial stenosis [6,7].

Indications

Lasers, particularly the Nd:YAG laser; have been utilized to treat a wide variety of conditions causing airway obstruction. Malignant tracheobronchial obstruction arising from primary lung carcinomas is the most common indication for Nd:YAG laser bronchoscopy (Figures 8.1–8.3). In the larger published case series, airway obstruction from bronchogenic carcinomas was the indication for therapy in 49–75% of patients [8–11]. The second most common indication for laser therapy is benign tracheal stenosis, usually occurring after translaryngeal intubation or tracheostomy, accounting for 10–27% of patients. Relief of obstruction due to malignancies metastatic to the airway was the indication for laser resection in 4–18% of cases. The Nd:YAG laser has been used for resection of benign tumors, including hamartomas, squamous papillomas, fibromas and lipomas [12]. Low-grade malignant tumors of the tracheobronchial tree, such as carcinoid and adenocystic carcinoma, have been successfully treated with Nd:YAG laser therapy [13,14]. The Nd:YAG

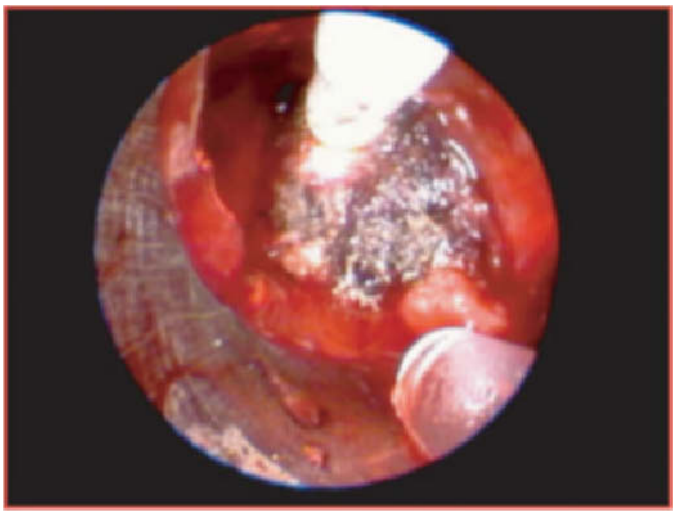

Figure 8.1 Laser photocoagulation of right mainstem bronchial tumor via rigid bronchoscopy.

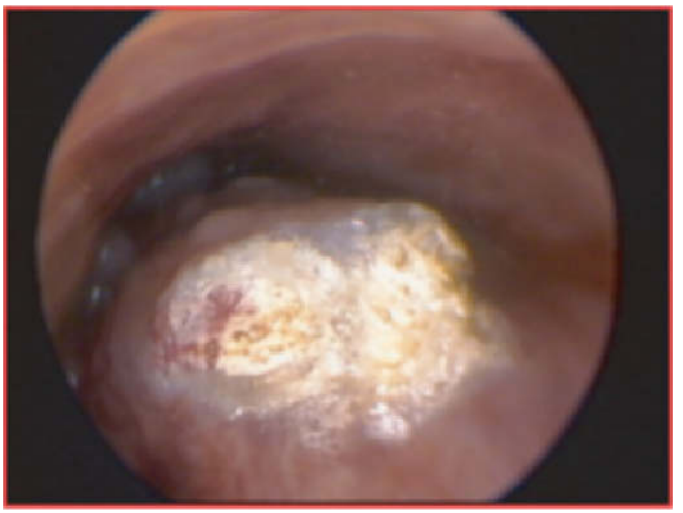

Figure 8.2 Laser photocoagulation of left mainstem bronchial tumor via rigid bronchoscopy.

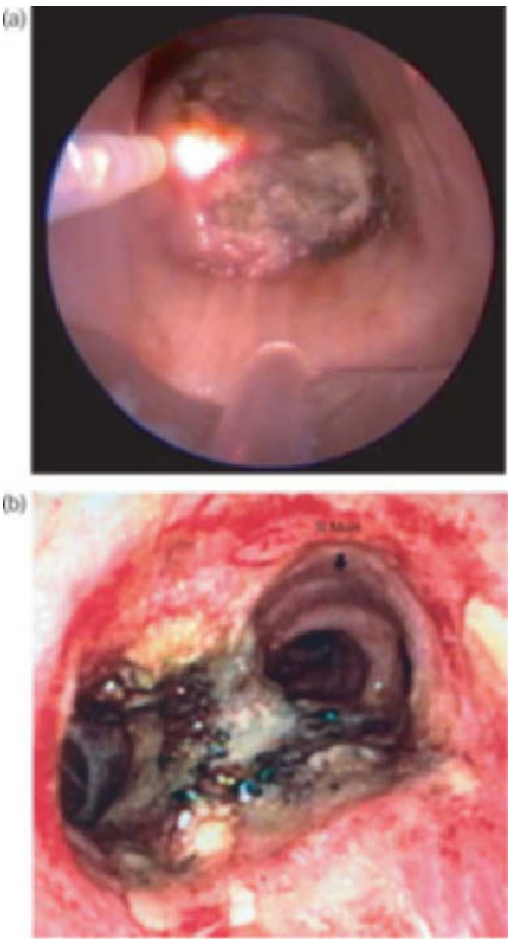

Figure 8.3 Laser photocoagulation of carinal tumor involving both mainstem bronchi via rigid bronchoscopy. (a) Beginning of laser resection. (b) Following laser resection.

laser has also been used to resect granulation tissue formation after lung transplantation and stent placement, suture granulomas, amyloidosis and broncholiths [15–18].

For malignant airway obstructions, laser bronchoscopy is typically used for palliation of symptoms. Better results have been obtained in treating lesions located in the trachea, mainstem bronchi and bronchus intermedius [10,11]. A number of factors influence whether or not the laser bronchoscopy will be successful. These are listed in Table 8.1. Dyspnea is the most common symptom requiring palliation. Relief of postobstructive pneumonia, cough and hemoptysis are other common indications. In some instances, laser resection of tumors in the distal mainstem bronchi may be done to stabilize the patient so that curative surgical resection can be subsequently performed. Laser bronchoscopy may also be used as curative therapy in patients with carcinoma in situ although this is not typically the primary therapy for this condition. Laser resection of benign tumors is often definitive therapy, and some patients with low-grade malignant tumors such as carcinoids may be provided with cure with laser therapy.

For benign tracheal and subglottic stenosis, laser bronchoscopy may provide effective therapy. The web type of stenosis, which consists of a concentric fibrotic stricture without tracheal wall involvement, can be treated with radial incisions of the web using the laser followed by bronchoscopic mechanical dilatation of the stenosis [19–21]. The bottleneck type of stenosis results from collapse of the tracheal wall and is not amenable to laser therapy. The complex type of stenosis consists of a combination of web formation and bottleneck stenosis with associated tracheomalacia. This type of stenosis may be amenable to treatment with a combination of laser resection, mechanical dilatation and stent placement if the patient is not a candidate for a tracheal resection procedure. Laser bronchoscopy has also been utilized to treat tracheal stenosis and bronchial stenosis due to Wegener's granulomatosis, Bechet's syndrome, relapsing polychondritis and mycobacterial infection [22–24].

Contraindications

There are a number of potential contraindications to laser bronchoscopy [1,25]. Obstruction due to purely extraluminal disease is an absolute contraindication to laser bronchoscopy. Laser resection should not be performed when there is tumor involvement of adjacent structures such as the pulmonary artery and esophagus as fistula formation may occur. In general, complete airway obstruction precludes laser bronchoscopy as the bronchoscopist may laser through the wall of the airway rather than into the distal airway lumen. Obstruction of the corresponding segment of pulmonary artery by tumor may preclude any benefits of laser resection as recanalizing the airway to a segment of lung with

Table 8.1 Factors that influence success of laser bronchoscopy.

Favorable	*Unfavorable*
Large endobronchial component	Lesion extrinsic to airway
Polypoid lesion	Primarily submucosal
Lesion <4 cm	Lesion >4 cm
Confined to trachea and mainstem bronchi	Upper lobe or segmental bronchus
Visible distal lumen	Totally obstructed lumen
Duration of lung collapse <4–6 weeks	Duration of collapse >4–6 weeks
Blood flow to lung not compromised	Blood flow to lung compromised
Patient hemodynamically stable	Patient hemodynamically unstable
Patient has good performance status	Patient has very poor performance status

minimal blood flow will lead to an increase in dead space ventilation and worsening of dyspnea. Lack of functional lung distal to the obstruction secondary to damage from radiation fibrosis or chronic postobstructive pneumonia will also obviate any benefit from laser bronchoscopy. If the involved lobe or the lung has been collapsed for more than 4–6 weeks, successful reexpansion is unlikely. High oxygen requirements prior to the procedure increase the risk of airway fire during the procedure. Patients who are hemodynamically unstable should not undergo laser bronchoscopy until properly resuscitated. Laser resection should not be performed in patients with underlying coagulopathies until the coagulopathy is corrected. Patients who are extremely moribund are unlikely to benefit from laser bronchoscopy and consideration should be given for comfort care measures rather than performing an interventional procedure.

Complications

A number of potential complications may arise from laser bronchoscopy [1]. Perforation of the posterior tracheal wall may lead to a tracheoesophageal fistula. Perforation of the tracheobronchial wall with the laser can produce a pneumothorax or pneumomediastinum. Laser resection of a lesion that involves a major vascular structure or is immediately adjacent to a major vascular structure may cause a life-threatening hemorrhage. Obtaining and carefully reviewing a preoperative computed tomography (CT) scan to assist in planning the laser bronchoscopy can reduce the risk of this occurring. A large tumor mass, previous surgery or previous radiation therapy may significantly change the normal anatomic relationships. Systemic air embolism has been reported during laser bronchoscopy and is associated with development of a communication between the tracheobronchial tree and vasculature in the setting of the patient undergoing positive pressure ventilation [26,27]. Following resection of highly obstructing tracheal lesions, noncardiogenic pulmonary edema may rarely occur [28,29]. Bronchospasm and pneumonia may develop following laser bronchoscopy. Cardiovascular complications may occur during the procedure with the most common complications being supraventricular tachycardias and hypotension. Myocardial infarction and cardiac arrest has also reported in a very small number of patients. A rare but potentially catastrophic complication is endotracheal fire [30,31]. Materials that can ignite during laser bronchoscopy include the sheath of the flexible bronchoscope and the endotracheal tube (ETT). To reduce this risk, the inspired oxygen concentration (FiO_2) should be kept less than or equal to 40–50% during active laser use. Specially designed ETTs should be used for the procedure if performing the procedure with a flexible bronchoscope in an intubated patient. A recent *in vitro* study also demonstrated that silicone stents could be ignited by the Nd:YAG laser with oxygen concentrations greater than 40% [32]. Although many patients undergoing laser bronchoscopy have impaired respiratory function and significant underlying comorbidities, the incidence of complications is surprisingly low. The frequency of complications in six large studies is presented

Table 8.2 Incidence of complications following Nd:YAG laser bronchoscopy. Adapted from [25] with permission.

Author	*No. of treatments*	*Vessel perforations*	*Airway fire*	*Pneumothorax*	*Hemorrhage*	*Arrhythmias/MI*	*Death*	*Complications (%)*
Personne *et al.* [33]	2289	3	0	24	—	—	18	1.18
Dumon *et al.* [34]	1503	1	0	4	14	3	1	0.34
Cavaliere *et al.* [35]	2008	0	0	8	19	5	12	0.03
Mehta *et al.* [36]	330	1	1	5	5	2	4	2.12
Brutinel *et al.* [37]	176	3	0	1	10	—	3	2.27
Kvale *et al.* [38]	82	0	0	0	0	1	1	0.01
Total	*6388*	*8*	*1*	*42*	*48*	*11*	*39*	*5.95*

MI, Myocardial infarction.

in Table 8.2 with an overall complication rate of 0.99% and procedural-related mortality rate of 0.005% [25].

An issue for the bronchoscopy team and patient is the potential for retinal damage. The wavelength of light emitted by the Nd:YAG laser can be focused by the lens onto the retina with subsequent permanent loss of vision [39]. All personnel working in the room should wear goggles designed to protect the eyes from the laser beam. The patient should also wear protective goggles or have the eyes taped shut with overlying patches during the procedure. It is also possible for the Nd:YAG laser to cause severe thermal burns to the skin. The bronchoscopist and assistants should be certain that the laser is in standby mode when the laser fiber is not inserted through the bronchoscope and aimed at the target.

Anesthesia

The method for anesthesia for Nd:YAG laser bronchoscopy is dependent on the type of bronchoscopic technique employed. For rigid bronchoscopy, either intravenous agents or inhalational anesthetics can be administered. Intravenous general anesthesia is typically performed with propofol infusion alone or with or midazolam and/or fentanyl as adjunctive medications. With inhalational anesthesia, a closed ventilation system needs to be used. When the procedure is carried out through the open end of the rigid bronchoscope, a different type of ventilation is required. Some bronchoscopists prefer spontaneous assisted ventilation [40] while others use a Venturi jet ventilation technique [41,42]. For jet ventilation, either a manual system or a high frequency jet ventilator can be utilized [43]. For laser bronchoscopy using the flexible bronchoscope, conscious sedation can be given similarly to diagnostic bronchoscopy, or if the patient is intubated, intravenous general anesthesia can be performed.

Techniques for laser bronchoscopy

The Nd:YAG laser can be used with either with a flexible or a rigid bronchoscope, and the choice of which bronchoscope to use has generated many debates in the literature [44,45]. The major advantage of the flexible bronchoscope is that most pulmonologists are familiar and proficient with the flexible bronchoscope. The flexible bronchoscope provides better access to distal airway lesions. Aiming of the laser fiber is typically easier with the flexible bronchoscope. Laser bronchoscopy using the flexible bronchoscope can be performed outside the operating room with conscious sedation and topical anesthesia, which can be more convenient and potentially less costly than rigid

Table 8.3 Dumon's 10 commandments of safe Nd:YAG laser resection. Adapted from [46] with permission.

1	Know the anatomic danger zones: aortic arch, pulmonary artery and esophagus being the main hazard areas.
2	Have a well-trained laser team, including an anesthesiologist specialized in light general anesthesia and two assistants drilled in emergency response procedures.
3	Screen patients carefully: any endoluminal growth is amenable to laser resection but purely external compression is beyond the reach of the technique.
4	Use the rigid bronchoscope technique for any high-grade obstruction, especially if malignancy is involved.
5	Monitor blood gases and cardiac performance. At the least sign of hypoxemia, interrupt treatment long enough to oxygenate the patient, if necessary under closed-circuit conditions.
6	Fire the laser parallel to the wall of the airway; never aim directly into it.
7	Coagulate at will but avoid using the laser at high power settings; mechanical resection after laser coagulation is preferable to laser resection alone whenever possible.
8	Do not neglect hemorrhage, for even slow bleeding will lead to hypoxemia if left unattended.
9	Terminate each procedure with a thorough laser irradiation of the resected area and a tracheobronchial toilet to remove all secretions and/or debris.
10	Keep the patient under observation in a specially outfitted recovery room for a reasonable period of time.

bronchoscopy, which is performed in the operating room and requires general anesthesia.

Rigid bronchoscopy offers significant advantages, however, over flexible bronchoscopy. In general, control and maintenance of the airway is better with the rigid bronchoscope. The larger diameter of the rigid bronchoscope and use of larger suction catheters through the bronchoscope offers a clearer visual field. Tumor can be more easily mechanically debulked using larger forceps and the bronchoscope itself. In cases of high-grade obstruction of the central airway, the rigid bronchoscope can be used to core through the lesion and quickly establish a patent airway. Control of bleeding is better with the rigid bronchoscope as tamponade of the bleeding site can be performed with the barrel of the bronchoscope. Typically, procedures performed using the rigid bronchoscope require less time than when using the flexible bronchoscope alone.

Before beginning to perform laser bronchoscopy, it is important to be familiar with the relationships between the tracheobronchial tree and major structures in the thorax. One should keep in mind that the volume of the tracheobronchial tree is only approximately 150 mL. Thus, even a small amount of blood or secretions can significantly impact oxygenation and lead to cardiac arrhythmias, myocardial ischemia and cardiac arrest. It is critical to maintain a clear airway and effective ventilation. Oxygenation should be monitored with pulse oximetry throughout the procedure. The FiO_2 should be kept at or less than 40–50% during active use of the laser and it is prudent to confirm this with the anesthesiologist before using the laser. All personnel should be wearing protective eyewear. Guidelines for safe laser resection are provided in Tables 8.3 and 8.4.

Table 8.4 Mehta's "Rule of Four" for safe Nd:YAG laser resection through the flexible bronchoscope. Adapted from [36] with permission.

Duration of collapse	<4 weeks
Length of lesion	<4 cm
Distance	
ETT to lesion	>4 cm
Fiber tip to lesion	4 mm
Bronchoscope to fiber tip	4 mm
FiO_2	<40%
Power settings	
Noncontact	40 W
Contact	4 W
Pulse duration	0.4 s
Number of pulses between cleaning	40
Operating time	<4 h
Laser team	4

For rigid bronchoscopy, the patient is intubated with the bronchoscope and it is placed near the lesion. Visualization is obtained through a rigid optical telescope passed through the bronchoscope and attached to a display monitor. The laser fiber and suction catheter are then passed through the open end of the bronchoscope or through special

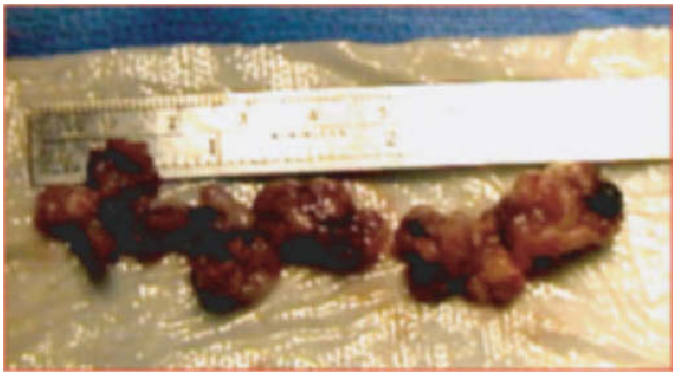

Figure 8.4 Tumor fragments following laser photocoagulation and mechanical coring with rigid bronchoscope.

ports in the bronchoscope depending on the preference of the operator and which rigid bronchoscope is used. The laser fiber is aimed at the lesion by manipulation of the rigid bronchoscope. Although the rigid bronchoscope is not flammable, the laser fiber should extend beyond the edge of the bronchoscope so that the beam is not reflected to an unintended position. Power settings are typically set at 20–40 W with a pulse duration of 0.4–1 s. The power setting of the laser and distance of the tip of the laser fiber to the tissue determine power density at the target site. Devascularization and photocoagulation are obtained by positioning the fiber about 1 cm from the lesion while charring and vaporization are achieved by placing the fiber 4 mm from the lesion. The initial goal of laser application should be photocoagulation of the entire tumor to reduce bleeding. Following this, the tumor can be debulked with the bronchoscope or biopsy forceps (Figure 8.4). Alternatively, some bronchoscopists prefer to vaporize the tumor mass after photocoagulation to reduce the size of the mass and further devascularize the tissue, followed by mechanical debulking. Care should be taken not to perforate the wall of the airway with the bronchoscope. To avoid perforation, the laser beam should be fired tangentially to the airway wall in a continually scanning fashion. After the tumor is debulked, the base of the lesion is thoroughly coagulated. At the end of the procedure, secretions and residual debris in the airways are cleared with washing and suctioning.

For flexible bronchoscopy, the process is similar. Some bronchoscopists prefer to intubate all patients routinely while others do so only if the patient's condition warrants such. If the patient is intubated, an ETT designed for use during laser procedures should be utilized. Power settings are typically 30–40 W with a pulse duration of 0.4–1 s. Care must be taken to have the laser fiber away from the tip of the bronchoscope to prevent ignition of the bronchoscope sheath. The lesion is initially photocoagulated over the entire surface with the initial applications at the tumor base to control bleeding. Because mechanical debulking is more difficult with the flexible bronchoscope, more extensive tumor vaporization must typically be performed. Tumor fragments can be removed with biopsy forceps or polypectomy snare as well as by applying suction to the bronchoscope to keep the tumor fragment in contact with the bronchoscope and then removing the bronchoscope from the airway.

Outcomes

Many large series have demonstrated that Nd:YAG laser bronchoscopy can be performed safely and with improvements in airway diameter in the vast majority of patients [33–38]. Although laser bronchoscopy has been used extensively for malignant and benign tracheobronchial obstruction, there are no randomized controlled trials that prove a survival benefit for patients treated with this modality. Improved survival in patients treated with laser bronchoscopy compared to historical controls treated with radiation therapy has been noted by some authors [37,47]. In a study of 47 patients treated with Nd:YAG laser resection for bronchogenic carcinoma, Desai *et al.* reported no significant difference overall between patients who received both laser resection and radiation therapy compared with patients who received radiation therapy

alone although a significant survival benefit was noted in 15 patients who underwent emergency laser resection versus the 11 patients who were treated with emergency radiotherapy [48]. Some case series have observed that survival time is greater in patients who have had successful airway recanalization with laser bronchoscopy compared to patients who had unsuccessful restoration of airway patency [49,50]. Laser bronchoscopy can also provide benefit in patients who require mechanical ventilation. Stanopoulos *et al.* [51] reported their experience in treating 17 patients with respiratory failure requiring mechanical ventilation from malignant airway obstruction. Most patients had non-small cell lung cancer. The duration of mechanical ventilation ranged from 1 to 25 days prior to intervention. The patients were treated with Nd:YAG laser resection via rigid bronchoscopy. In 9 of the 17 patients, successful extubation was achieved. Endobronchial tumor obstruction was the predominant finding in patients who were successfully extubated while extrinsic airway compression and submucosal disease were more prominent in patients unable to be weaned from mechanical ventilation. The median survival was 98 days (range 5–770) for the successfully extubated patients versus 8.5 days (range 1–15) for patients unable to be weaned from mechanical ventilation.

Given that the majority of interventional pulmonary procedures are performed for palliative purposes, it can be argued that survival data may not be the best measure of effectiveness of this treatment modality. Indeed, the more important question is whether laser bronchoscopy can be demonstrated to provide benefits in pulmonary function and patient quality of life. Data regarding changes in pulmonary function after laser bronchoscopy is presented in Table 8.5. Unfortunately, most studies to date have reported changes in performance status and dyspnea scores rather than true quality of life measures. This data is presented in Table 8.6.

Electrocautery

Electrocautery, also referred to as diathermy and electrosurgery in the literature, is the use of electrical current to generate thermal destruction. As the electrical current passes through the tissue, tissue resistance to current flow produces heat. High frequency alternating current of 10^5–10^7 Hz is used to avoid activation of nerves and muscles. At temperatures of 70°C tissue coagulates. At temperatures of 100°C intracellular and extracellular water vaporizes and the tissue dries out while at 200°C carbonization occurs [60]. Coagulation is produced by using high amperage and low voltage whereas vaporization is produced by using high voltage and low amperage. Tissue effects are also mediated by contact between the electrocautery probe and tissue. With direct contact of the probe, superficial coagulation tends to occur. When the probe is not in contact with the tissue and current is applied, arcs between the probe and tissue occur causing deeper coagulation.

Two different types of electrocautery probes are available, monopolar and bipolar. For bronchoscopic applications, monopolar systems have been more widely used. With monopolar systems, the electron flow is focused toward the area of contact between the probe and tissue. Unipolar systems require the electrocautery generator, bronchoscope, and patient to be grounded to complete the electrical circuit. If proper grounding is not performed, shocks and burns can occur. The patient is grounded with an electrode pad placed on the extremity nearer to the site of electrocauterization. During use of monopolar systems, an insulated bronchoscope is suggested to reduce risk of shock and burn to the bronchoscopist. Device companies have produced insulated bronchoscopes designed for safe usage with electrocautery procedures. Probes are available for use both with the rigid and flexible bronchoscope. Olympus has recently developed a series of different electrocautery probes and snares for use specifically with the flexible bronchoscope (Figure 8.5).

With bipolar electrodes, current flows between a set of electrodes at the tip of the probe. This system obviates the need for grounding of the patient. Bipolar electrocautery has been used extensively for gastroenterology applications, but little has been published regarding use for bronchoscopic procedures [61,62]. The authors have employed a bipolar electrocautery system through the flexible bronchoscope with excellent results (Figure 8.6).

A relatively new development is argon plasma coagulation (APC). APC utilizes ionized argon

Table 8.5 Changes in pulmonary function after laser resection for airway stenosis.

Author	*Number of patients*	*Measurement*	*Findings (mean values)*
Gelb and Epstein [52]	27, incomplete obstruction of trachea/main bronchus	FEV_1	52–74% of predicted*
		FVC	64–77% of predicted*
	19, complete obstruction of main bronchus	FEV_1	44–48% of predicted‡
		FVC	46–59% of predicted*
Gelb and Epstein [53]	70, incomplete obstruction of trachea/main bronchus	FEV_1	45–60% of predicted*
		FVC	57–69% of predicted*
	23, complete obstruction of main bronchus	FEV_1	47–52% of predicted†
		FVC	50–55% of predicted†
Gelb *et al.* [54]	10, main bronchus	FEV_1	45–72% of predicted
		FVC	51–84% of predicted
		$Vmax_{50\text{-}E}$	31–75% of predicted
		$Vmax_{50\text{-}I}$	57–85% of predicted
Gelb *et al.* [55]	13, trachea	FEV_1	46–72% of predicted
		FVC	77–82% of predicted
		$Vmax_{50\text{-}E}$	25–56% of predicted
		$Vmax_{50\text{-}I}$	44–64% of predicted
George *et al.* [56]	28, main bronchus/LB	FEV_1	Increased by 220 mL*
		FVC	Increased by 390 mL*
		Ventilation‡	Increased 24–36%*
		Perfusion‡	Increased 25–31%*
		6 min walk	443–512 m*
Kvale *et al.* [38]	6, benign tracheal	FEV_1	Increased 358 mL
		FVC	Increased 183 mL
	6, malignant-no prior tx	FEV_1	Increased 428 mL
		FVC	Increased 610 mL
	9, malignant-prior tx	FEV_1	Increased 181 mL
		FVC	Increased 115 mL
Waller *et al.* [57]	142, trachea/main bronchus/LB	FEV_1	Increased 300 mL
		FVC	Increased 110 mL
Mohsenifar *et al.* [58]	11, trachea/main bronchus	FEV_1	35–69% of predicted
		FVC	55–83% of predicted
		$Vmax_{50\text{-}E}$	0.87–1.6 L/s
		$Vmax_{50\text{-}I}$	1.8–2.6 L/s
Gilmartin *et al.* [59]	17, trachea/main bronchus	FEV_1	Increased 360 mL*
		PEFR	Increased 0.65 L/s*
		Perfusion‡	Increased 10–13%†

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LB, lobar bronchus; PEFR, peak expiratory flow rate; tx, treatment; $Vmax_{50\text{-}E}$, mean maximal expiratory flow at 50% of forced expiratory volume; $Vmax_{50\text{-}I}$, mean maximal inspiratory flow at 50% of forced inspiratory volume.

*$p < 0.05$.

†$p =$ not significant.

‡Quantitative scintigraphic data of involved areas.

Table 8.6 Performance status and dyspnea after laser resection for malignant obstruction.

Author	*Number of patients*	*Measurement*	*Findings (mean scores)*
Gelb and Epstein [52]	27 incomplete obstruction	Karnofsky score	Improved 41–57*
		MRC DI	Improved 3.7–2.8*
	19, complete obstruction	Karnofsky score	Improved 30–35
		MRC DI	Improved 3.7–3.4
Gelb and Epstein [53]	70, incomplete obstruction	Karnofsky score	Improved 42–59*
		MRC DI	Improved 3.6–2.5*
	23, complete obstruction	Karnofsky score	Improved 38–43
		MRC DI	Improved 3.5–3.3
Ross *et al.* [49]	55, successfully treated	Karnofsky score	Improved 41–60*
	14, unsuccessfully treated		Improved 45–54*
George *et al.* [56]	28	Karnofsky score	Improved 67–78
		MRC DI	Improved 3.5–2.7*
		VAS-B	Improved 57–71*
		VAS-W	Improved 57–71*

MRC DI, Medical Research Council dyspnea index; VAS-B, visual analog scale for breathlessness; VAS-W, visual analog scale for well-being.
*$p < 0.05$.

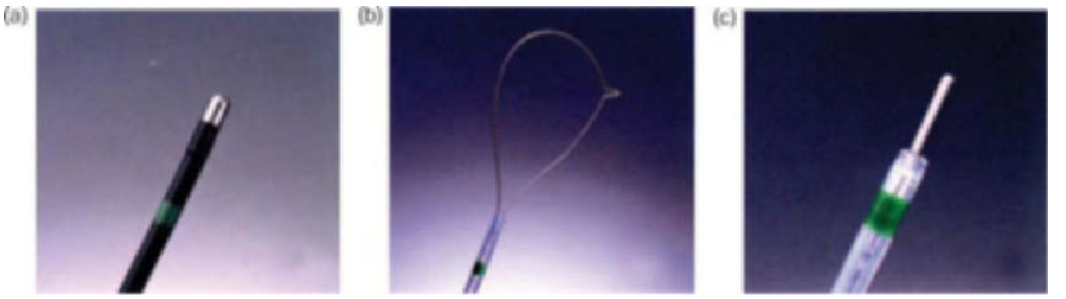

Figure 8.5 Electrocautery devices for use with monopolar systems (Olympus Inc.). (a) Blunt electrocautery probe. (b) Electrocautery snare. (c) Electrocautery knife.

Figure 8.6 Bipolar electrocautery probe with injection needle (Boston Scientific Corp.).

gas to conduct electrical current between the probe and the tissue. APC is thus a noncontact mode of electrocautery. The APC probe can be passed through the working channel of a flexible bronchoscope and a system is currently available for use in the United States (ERBE USA, Inc.). One limitation of APC is that depth of penetration is 3 mm which somewhat limits its effectiveness for

treating bulky tumors. It is effective for tumors that are more superficial and for treating bleeding sites.

Indications

Electrocautery has primarily been used for palliative treatment of malignant airway obstruction and has been effective for this indication, both with rigid and flexible bronchoscopic approaches (Figures 8.7 and 8.8) [63–73]. Radiographically occult lung cancers and intraluminal typical carcinoids have been cured with electrocautery [74–76]. Electrocautery has been used to treat benign tumors such as hamartomas, lipomas, leiomyomas and squamous papillomas [63,65,69,72,73]. Benign tracheal stenosis and bronchial stenosis have also been effectively treated [63,77]. Additional applications for electrocautery include amyloidosis, respiratory papillomatosis and granulation tissue after lung transplantation and stent placement [63,69]. APC has been successfully used for palliation of malignant airway obstruction, hemoptysis management, treatment of granulation tissue and management of recurrent respiratory papillomatosis [78–81].

Contraindications

Contraindications to electrocautery are similar to that for laser therapy. Factors similar to those noted for laser bronchoscopy will be influential on the success of the procedure (Table 8.1). Electrocautery is not effective for purely extrinsic airway compression. Tissue penetration with electrocautery is less than that with the Nd:YAG laser and there is theoretically less risk of bronchial wall perforation and fistula formation into nearby structures. Nonetheless, it is prudent to observe the same precautions as with laser resection if the lesion is contiguous with the pulmonary artery and esophagus. Given the potential for airway fire with this technique, patients who require high levels of FiO_2 may not be appropriate for electrocautery. Patients should be hemodynamically stable. Any

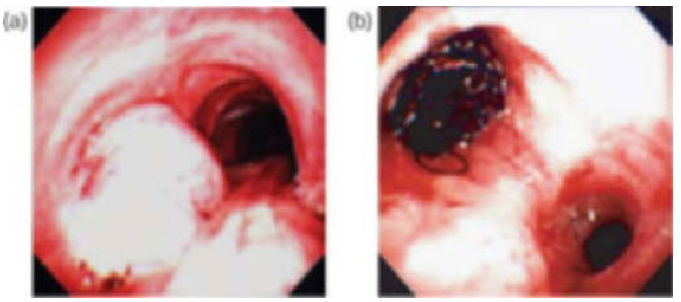

Figure 8.7 Left mainstem bronchial tumor. (a) Prior to electrocautery resection. (b) Following electrocautery resection via flexible bronchoscopy and stent placement.

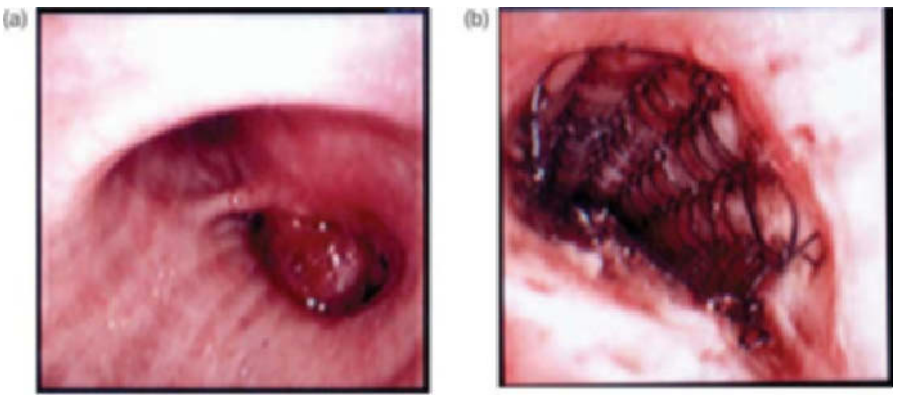

Figure 8.8 Right mainstem bronchial tumor. (a) Prior to electrocautery resection. (b) Following electrocautery resection via flexible bronchoscopy and stent placement.

underlying coagulopathy should be corrected prior to the procedure.

Complications

The complication rate with electrocautery appears to be low. Bleeding is the most common complication although massive hemorrhage is rare due to the coagulation properties of electrocautery. Homasson noted bleeding in 2.5% of the 270 patients treated with electrocautery although one patient did die of massive hemoptysis 3 days after the procedure [60]. Two cases of tracheal fire have been reported during electrocautery procedures in which high levels of supplemental oxygen were administered [72,82].

Technique of electrocautery

Electrocautery may be performed with either the rigid or the flexible bronchoscope. The authors' preference is to use flexible bronchoscopy and conscious sedation in patients appropriate for electrocautery. In general, patients with high-grade obstructing lesions of the trachea and tumors involving the carina with severe bilateral mainstem bronchial involvement are not good candidates for electrocautery using the flexible bronchoscope technique. If a monopolar system is used, the patient needs to be grounded. If a flexible bronchoscope is used with a monopolar system, the bronchoscope should be an insulated model. Typically, a power setting of 30–50 W is used with blunt probes while 10–30 W is usually sufficient when using the snare. Several electrocautery generators not only allow adjustment of wattage but also current modes including cut, coagulate and blend. The cut mode uses high current with low voltage while the coagulation mode produces low current with high voltage. The cut mode achieves the greatest vaporization of tissue and is commonly used for tumor resection. The blend mode combines coagulation and cutting and is selected when the snare is employed. During active use of electrocautery, the FiO_2 should be kept at 40–50% or less.

Blunt-tipped probes are available for use with the rigid and flexible bronchoscopes. A rigid cutting loop is also available for the rigid bronchoscope. The blunt probes and the cutting loop are used for resection of large, broad-based lesions. The technique of electrocautery resection is similar to that of the contact mode with the Nd:YAG laser. The probe is placed in light contact with the surface of the lesion and current applied in 1–2 s intervals. The probe should be moved periodically to treat the entire surface of the lesion. Care should be taken not to heavily treat areas close to normal bronchial mucosa as damage to underlying cartilage and subsequent stenosis has been noted in animal studies [83]. To maximize the tissue effect, it is helpful to keep the treatment area free of blood and mucus. The probe needs to be cleaned periodically to remove the layer of carbonized tissue that often develops on the surface of the probe and reduces the efficiency of electrocautery treatment. In some cases of bulky tumors, a residual mass will remain after treating the surface of the tumor. The residual mass can then be mechanically debulked with biopsy forceps or the bronchoscope and then removed. For larger pieces of tumor, the tissue can be removed by grasping the tissue with biopsy forceps or applying continuous suction to affix the tumor to the bronchoscope and then removing the bronchoscope along with the tumor fragment.

The loop snare, which is similar to a polypectomy snare, is useful to resection pedunculated lesions. In addition, some bronchoscopists will use the snare to resect portions of bulky tumors. The wire snare is passed beyond the lesion and then opened in the distal lumen. The open loop is then pulled proximally to pass the loop over the lesion and directed toward the base of the lesion with the bronchoscope. The loop is gently closed around the lesion and blend mode current is applied as the snare is completely closed. Closing the snare loop too quickly will cause mechanical cutting as opposed to cutting with the electrocautery current. This may lead to increased bleeding. An electrocautery knife is also available for use with the flexible bronchoscope. The knife can be employed to make radial incisions for management of benign stenosis, similar to the Nd:YAG laser.

APC electrocautery can also be used with the flexible bronchoscope. APC is a noncontact method with the probe placed 3–5 mm away from the lesion. The probe should be extended 5–10 mm beyond the tip of the bronchoscope to prevent thermal damage to the bronchoscope. The current will flow from the probe tip along the path of least resistance to the bronchial wall in a lateral fashion

rather than along a straight path. The surface of the lesion is then essentially sprayed with the argon beam. As the treatment area becomes coagulated and less electrically conductive, the APC beam will then spread to adjacent tissue that is less resistant to current flow. Tumor is removed through sequential cauterization of the surface followed by removal of the coagulated surface of the tumor with biopsy forceps or suctioning.

Outcomes

Very few studies have been published evaluating changes in quality of life dimensions or pulmonary function after electrocautery resection or APC; instead, most have focused on technical aspects and success rate of lesion resection. In a series of 56 patients treated with electrocautery, Homasson reported improvement in dyspnea in 67% and control of hemoptysis in 75% of patients [60]. No further information was provided about the patient series. Morice and colleagues treated 60 patients with 70 applications of APC via flexible bronchoscopy; 43 patients had bronchogenic carcinoma, 4 had endobronchial metastases and 3 had benign disease [78]. Improvement in dyspnea was reported as excellent after 37 procedures (53%) and moderate after 32 procedures (46%). Hemoptysis was controlled in all 56 patients with this symptom. Sutedja and coworkers treated 17 patients with malignant airway obstruction with electrocautery resection via flexible bronchoscopy [67]. Pulmonary function tests (PFTs) were obtained in 8 patients with 2 having greater than a 15% improvement from baseline values. Blood gases significantly improved in 2 of 12 patients. Dyspnea was improved in 8 of 11 patients (73%) and hemoptysis in all 4 patients.

Ledingham and Goldstraw treated 15 patients with recurrent central airway obstruction from bronchogenic carcinoma after previous external beam radiotherapy with electrocautery resection (diathermy) and radioactive gold grain implantation via rigid bronchoscopy [70]. All of the 11 patients alive 1 month after intervention had improved symptomatically. FEV_1 improved in all 11 patients from 30 to 120% (mean 69%). Reexpansion after total lung collapse was noted in 2 of 2 patients and after lobar collapse in 3 of 6 patients. Petrou and colleagues treated 29 patients with central airway obstruction with electrocautery resection in combination with stent placement in 9 patients and radioactive gold grain insertion in 1 patient via rigid bronchoscopy [69]. Twenty-four patients had malignant tumors, 3 had benign neoplasms, 1 had amyloidosis, and 1 had a post-intubation stricture. All 9 patients requiring urgent treatment and 19 of the 20 patients treated electively reported symptomatic improvement. PFTs were available in 8 patients with a mean improvement in FEV_1 of 53.1% (range 8–142%) and in FVC of 20.6% (range 0–100%).

van Boxem and coworkers [64] recently published a retrospective study comparing 14 patients treated with Nd:YAG laser resection to 17 patients treated with electrocautery for airway obstruction due to nonsmall cell lung cancer. Only six of the electrocautery patients required the procedure to be performed under general anesthesia. Improvement in symptoms, primarily dyspnea, was observed in 71% of patients treated with Nd:YAG laser versus 76% of patients treated with electrocautery. Mean survival was 8.0 months and 11.5 months, respectively. The laser group required an average of 1.1 treatment sessions per patient while the electrocautery group averaged 1.2 treatment sessions. Average treatment costs were $5321 for the laser group compared to $4920 for the electrocautery group. This difference in costs, however, can be attributed to a longer average hospital stay for the patients treated with Nd:YAG laser while awaiting access to the operating room and Nd:YAG laser unit.

Cryotherapy

Cryotherapy is the use of controlled, local application of cold material to tissues to produce tissue destruction via the cytotoxic effects of freezing. The effects of freezing related damage occur at multiple levels including the molecular level, intracellular and cellular level and tissue level. Based upon experimental studies the following series of events is thought to occur as cells are frozen and then thawed: (a) between $-5°C$ and $-15°C$ ice crystals form in the extracellular space, (b) as the extracellular ice crystals form, the extracellular space becomes hypertonic relative to the intracellular space, (c) the osmotic gradient causes

the intracellular solute concentration to increase and the pH to fall which damages intracellular proteins and organelles, (d) with further cooling, particularly rapid cooling, intracellular ice crystals begin to form which mechanically disrupt the nucleus and organelles, (e) as the temperature continues to decrease, the eutectic point is reached and complete intracellular crystallization and solidification occurs, and (f) slow thawing induces recrystallization with the formation of large crystals that damage intracellular organelles and membranes [84].

In addition to these immediate effects, vascular changes ensue following tissue freezing which lead to the delayed effects of cryotherapy. These vascular changes consist of vasoconstriction of arterioles and venules, platelet aggregation, increased blood viscosity and microthrombi deposition along the endothelium. These alterations lead to vessel thrombosis and further ischemic injury to the tissue. Together, the cellular and vascular effects of cryotherapy lead to delayed tissue necrosis.

The extent of tissue damage is determined by the rate of cooling, the rate of thawing, the lowest temperature achieved, number of freeze–thaw cycles performed and the type of tissue being frozen [85,86]. In general, rapid cooling, slow thawing and multiple freeze–thaw cycles leads to maximal tissue destruction. Freezing to −30° to −40° at a rate of 100°C per minute will cause greater than 90% cell death and effective lesion destruction [87]. Tissue sensitivity to cryotherapy is related to the amount of free water content. Skin, mucosal surfaces, nerve fibers and granulation tissue tend to be cyrosensitive while bone, fat, cartilage and fibrous connective tissue tend to be cryoresistant. Tumor cells may be more cryosensitive than normal cells. There have been suggestions that cryotherapy may induce immunologic responses that have antitumoral effects although further studies are necessary before any definite conclusions can be made about this aspect of cryotherapy [85,86].

Materials used as cooling agents are termed cryogens. For bronchoscopic applications, liquid nitrogen and nitrous oxide have been utilized. Liquid nitrogen is readily available but requires storage in a vacuum-insulated container to reduce evaporative losses. As liquid nitrogen passes through the transfer line, it evaporates and the gas phase comes into contact with the tip of the cryoprobe. The transfer line and probe, except for the tip, are insulated so that evaporation and cooling occurs primarily at the tip of the cryoprobe. Although a low temperature of −196°C is achieved, cooling of the tip is not as rapid as with nitrous oxide. Thawing is also slower as this does not begin until all of the liquid nitrogen in the transfer line has been removed. Nitrous oxide is the most commonly employed cryogen. It is stored in high-pressure cylinders at room temperature in a liquid phase. When the nitrous oxide is transferred to the tip of the cryoprobe, it expands through a small nozzle from a high pressure to atmospheric pressure and changes from the liquid phase to a gas phase. This produces a rapid cooling at the cryoprobe tip via the Joule–Thomson effect to a temperature of −89°C. Because the cryoprobe does not require thermal insulation, small diameter probes have been manufactured which allow use through a flexible bronchoscope.

Cryotherapy machines consist of three parts: the console, the cryoprobe and transfer line that connects the console and gas cylinder to the probe. Several companies including Erbe in Germany, Date in France, Spembly Medical in England and MST in the Czech Republic manufacture cryotherapy equipment. All manufacturers use nitrous oxide as the cryogen, except for MST, which uses liquid nitrogen. The Erbe cryotherapy system is FDA approved for use in the United States. Cryoprobes are available as rigid, semirigid and flexible types (Figure 8.9). The rigid and semirigid cryoprobes are designed for rigid bronchoscopy

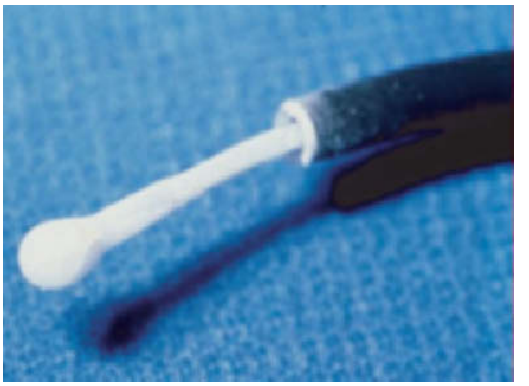

Figure 8.9 Cryoprobe with ice ball at the end of the probe.

while the flexible cryoprobes can be used with the flexible bronchoscope. Rigid probes are available with straight tips and with a right-angled tip. The straight tip probe is used for lesions in the trachea, mainstem bronchi and basilar segments of the lower lobes while the right-angled tip probe is used for lesions in the upper lobes and superior segment of the lower lobes. Due to its size, a flexible bronchoscope with a 2.6 or 3.2 mm working channel is required to use the flexible cryoprobe. The larger rigid and semirigid probes offer the advantage of being able to treat larger areas and faster freeze–thaw cycles, which decreases the procedure time.

Indications

Malignant airway obstruction has been the most common indication for cryotherapy. Several studies have reported cryotherapy to be safe and effective in this circumstance [88–93]. Cryotherapy has also been used to treat superficial bronchogenic carcinomas [94] and typical carcinoid tumors [95]. Successful treatment of granulation tissue at the site of anastomosis following lung and heart–lung transplantation has been reported [96]. There is one case report of successful treatment of tracheobronchial amyloidosis with cryotherapy [97]. In addition, cryotherapy has been noted to be useful to remove airway foreign bodies and blood clots [98].

Other potential indications for cryotherapy include granulation tissue secondary to stent placement and respiratory papillomatosis. In general, a fibrous stenosis is resistant to treatment with cryotherapy, and therefore there is limited use for cryotherapy in treating benign tracheal stenosis due to intubation. The utility of cryotherapy in treating benign tracheobronchial stenosis secondary to inflammatory airway conditions is unclear at present.

Contraindications

In general, there are few contraindications to cryotherapy other than the suitability of the patient to undergo flexible or rigid bronchoscopy. A notable exception to this is the presence of a high-grade obstructing tracheal tumor. Because the effects of cryotherapy are delayed and immediate airway patency is not achieved, this type of lesion should be managed with another modality. Some bronchoscopists, however, will treat the residual tumor base with cryotherapy following mechanical and/or laser debulking [98]. The same factors that influence success of laser bronchoscopy are also applicable to cryotherapy (Table 8.1). Cryotherapy is not effective for conditions causing pure extrinsic airway obstruction. The patient should be hemodynamically stable and not coagulopathic prior to performing the procedure.

Complications

Reported complications have included bleeding, pneumothorax and bronchospasm [90,93]. One case of cardiopulmonary arrest during the procedure has been reported [93]. Although the incidence of complications from cryotherapy appears to be low, one study of 153 patients with malignant airway obstruction did note an overall complication rate of 7.2% [90]. With the delayed tissue effects of cryotherapy, a potential complication is airway obstruction from tumor slough.

Techniques for cryotherapy

Cryotherapy may be performed using rigid bronchoscopy or flexible bronchoscopy. With rigid bronchoscopy, either the rigid, semirigid or flexible cryoprobes may be employed although the rigid and semirigid probes offer the advantage of larger probe tips and area of treatment per each freeze–thaw cycle. The metallic tip of the cryoprobe is placed on the surface of the lesion or pushed into it. Three freeze–thaw cycles are carried out at each site. Some bronchoscopists utilize a freezing time of 30 s per cycle [98] while others prefer a freezing time of 3 min [95]. After freezing, the probe is allowed to thaw until the probe separates from the tissue. If the cryotherapy probe is equipped with a device for measuring impedance as a means for assessing the degree of tissue freezing, the cryogen is applied to the probe until the impedance plateaus between 250 and 500 kΩ. Thawing is then allowed to occur until the impedance falls to 50 kΩ. After three freeze–thaw cycles, the probe is then moved 5–6 mm and another three cycles are performed in the adjacent area. The points of cryotherapy application are thus staggered with an overlap of the frozen zones. This process is continued until the

entire visible surface of the tumor has been frozen. It is necessary to remove any slough or necrotic tissue with the suction catheter or biopsy forceps to prevent insulation of the tumor. The process is similar for performing cryotherapy with the flexible bronchoscope. Only the flexible probe can be used, however, and a bronchoscope with a 2.6 or 3.2 mm working channel should be employed to allow passage of the probe. The cryoprobe should be kept about 4 mm away from the bronchoscope to prevent freezing of the scope.

At the end of the procedure the tumor may appear relatively undamaged. Because the vessel thrombosis effect of cryotherapy is delayed for several hours, it is prudent not to mechanically debulk the tumor after freezing of the lesion has been completed [98]. No special care is required immediately following the cryotherapy session. Repeat bronchoscopy is performed in 1–2 weeks to remove any tissue slough and reassess if further cryotherapy is required.

Outcomes

A number of studies have noted improvements in symptoms and pulmonary function with the use of cryotherapy. Maiwand treated 153 patients with cryotherapy under rigid bronchoscopy for malignant tracheobronchial obstruction [90]. The Karnofsky performance score improved by 54.6%; 76 patients had increases in performance status. Dyspnea improved in 85 of 133 patients (64%), cough in 82 of 120 patients (68%), hemoptysis in 51 of 55 patients (93%) and chest pain in 25 of 45 patients (56%). PFTs demonstrated an increase in FEV_1 by 65% (1.34–1.45 L) ($p = 0.001$) and FVC by 58% (1.93–2.02 L) ($p = 0.035$) 35. In a separate report by Maiwand describing 600 patients being treated with cryotherapy for malignant lesions, dyspnea improved in 66% (451 patients), cough in 64% (348 patients), hemoptysis in 65% (252 patients) and chest pain in 24% (96 patients) [86]. Two other studies by Maiwand and associates have reported changes in pulmonary function after cryotherapy via rigid bronchoscopy. In one study, 21 patients were treated for tracheal or bronchial obstruction from granulation tissue after lung or heart–lung transplantation [96]. PFTs were obtained in 20 patients. FEV_1 improved by 34% (mean change 285 mL) and FVC by 28% (mean change 372 mL) ($p < 0.001$ for both). In the second study, 33 patients underwent cryotherapy for malignant tracheobronchial stenosis [91]. Of 29 patients, 7 (24%) had an increase in FEV_1 and FVC although specifics were not provided. Six minute walking distance increased in 6 of 22 patients (27%). The MRC dyspnea score improved in 10 of 27 patients (37%) while hemoptysis improved in 6 of 9 patients (67%). Radiographic improvement of atelectasis was improved in 7 of 29 patients (24%).

Marasso and coworkers treated 234 patients with cryotherapy via rigid bronchoscopy [92]. Of the 243 patients, 190 had malignant stenoses and 44 had benign stenoses. Improvement of dyspnea was noted in 81% of patients (87 of 107) and hemoptysis in 93% (58 of 62). PaO_2 increased in 120 of 168 patients (71%). Resolution of lung or lobar atelectasis was noted in 69% of patients (78 of 115). Twenty-two patients with tracheobronchial obstruction, malignant in 20 and post-lung transplant anastomotic strictures in 2, had fiberoptic bronchoscopic cryotherapy performed by Mathur and associates [93]. Subjective improvement in dyspnea occurred in 12 of 17 patients (71%) and in all 5 patients with hemoptysis.

Summary

Laser bronchoscopy, electrocautery and cryotherapy are all highly effective therapy for the variety of conditions causing airway obstruction. None of these therapies is effective in treating extrinsic airway compression or lesions with predominantly submucosal infiltration. In this situation, one should consider stent placement. In general, it is more a matter of physician preference and training experience that leads to a selection of a particular modality rather than one technique being superior to another. There have been no randomized trials comparing these modalities.

Due to its long history of usage and large number of case series published in the literature, Nd:YAG laser resection has become the de facto gold standard to which other interventions are compared. The Nd:YAG laser is efficacious in relieving both malignant and benign airway stenoses. One advantage of the Nd:YAG laser is that immediate airway

patency is achieved which is important for patients with moderate to severe respiratory symptoms. Many physicians feel that the combination of rigid bronchoscopy with laser resection is the least time-intensive modality to treat airway obstruction. One aspect of laser bronchoscopy that may or may not be a disadvantage, depending on one's viewpoint, is that Nd:YAG laser equipment is not widely available and few pulmonologists are trained in this technique. Laser bronchoscopy has the steepest learning curve and requires more time to become proficient. In addition, Nd:YAG laser equipment is substantially more expensive to purchase than electrocautery and cryotherapy equipment. Nd:YAG laser therapy may be more expensive due to associated operating room and anesthesia charges.

Electrocautery can be successfully used to treat a number of malignant and benign airway conditions. Due to renewed interest in this modality occurring lately and electrocautery devices designed for use with the flexible bronchoscope recently being released, not as much literature has been published supporting the effectiveness of this technique. Electrocautery, like laser bronchoscopy, has the advantage of achieving immediate patency of the airway. Our experience has been similar to that noted by Coulter and Mehta [63]. For many lesions that we would have previously utilized Nd:YAG laser bronchoscopy, we are now successfully using electrocautery via the flexible bronchoscope under topical anesthesia and conscious sedation. Being able to perform these procedures in the bronchoscopy suite with conscious sedation may be more cost effective than laser resection although a formal study to answer this question has not been performed. Most hospitals already have electrocautery generators and the technique is easier to learn and potentially safer than laser bronchoscopy due to less tissue penetration. This may allow more pulmonologists to be able and available to palliate malignant airway obstruction. One potential disadvantage of electrocautery is that resection of bulky tumors may take longer than with the Nd:YAG laser.

Cryotherapy is also effective for malignant airway obstruction, low-grade or benign tumors and granulation tissue. It is not effective for fibrous stenosis and thus has limited utility in treating post-intubation and tracheostomy-related tracheal stenosis. Cryotherapy has the advantages of being able to be performed with the flexible bronchoscope using conscious sedation. It is a very safe modality and easy technique to learn. Cryotherapy can be a very helpful tool in the management of airway foreign bodies and for blood clot extraction. The main disadvantage of cryotherapy is the delayed tissue necrosis effect. Thus, unlike laser bronchoscopy or electrocautery, immediate airway patency is not achieved. Cryotherapy, therefore, should not be used for high-grade obstructions of the central airways. Unlike the Nd:YAG laser or electrocautery, coagulation of blood vessels does not occur immediately after cryotherapy application, which limits its utility for acute management of hemoptysis secondary to an endobronchial lesion.

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9

CHAPTER 9

Photodynamic therapy for endobronchial tumors: palliation and definitive therapy

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Introduction

Fundamental to pulmonary applications of photodynamic therapy (PDT) is the concept of using photochemical sensitizers and light of a particular wavelength to generate a photochemical reaction. A variety of photosensitizing agents can be used, all of which tend to be concentrated within tumor cells to a greater degree than in normal tissue. The agents themselves are inactive however. It is exposure to light that activates them. Activation leads to the generation of toxic oxygen radicals, cell death and eventual tumor necrosis. This review focuses on the use of PDT for treatment of early and advanced stage lung cancer, including the fundamental principles underlying PDT as well as its clinical applications.

Principles of PDT

In order for PDT to be effective, a number of necessary conditions must exist. First, the photosensitizers must have certain biochemical and biophysical characteristics in order to be selectively concentrated in tumor tissue and subsequently activated by light. Second, after the photosensitizers are concentrated in the tumor and activated by light, there must be a molecular mechanism to transduce this physical reaction into a biochemical process that leads to cell death and necrosis. Finally, proper technique and equipment must be used to deliver the drug and the light in a controlled fashion in order to reliably reproduce the desired effect in patients.

Biochemical and biophysical characteristics of photosensitizers

There are a wide variety of photosensitizing agents that have been studied and developed to varying degrees (Table 9.1). The goal is to develop an agent that is selective for tumors, has absorption spectra in a clinically useful range and has minimal side effects such as skin photosensitivity. These performance characteristics are determined by the biochemical and biophysical properties of the photosensitizer.

Photosensitizers must be able to attain high concentrations within tumor cells relative to the surrounding tissue. It is their biochemical properties that lead to this increased concentration of photosensitizers within tumor cells as compared to the surrounding tissue. A high tumor to normal tissue concentration ratio is desirable, since this minimizes side effects on normal tissue. Indeed, increased tumor concentrations of porphyrin-based photosensitizers were documented as far back as 1948 [1]. Newer derivatives of hematoporphyrin can reach even higher tumor to tissue concentration ratios, with increased fluorescence being detectable as early as 3 h following administration and peak concentration ratios being attained at 24–48 h [2–4].

However, the exact mechanism that leads to increased concentration in tumors remains unclear

Table 9.1 Agents used for photodynamic therapy.

Agents with clinical trials	*Comments*
Porfimer sodium (Photofrin; QLT Inc., Vancouver, Canada; Axcan Pharma, Birmingham, AL)	Several absorption peaks, absorbs more strongly at lower wavelengths, but 630 nm used to penetrate more deeply and to avoid interference from hemoglobin. Skin photosensitivity lasts 4–6 weeks. Depth of treatment is 3–5 mm.
Benzoporphyrin derivative (BPD) (Verteporfin; QLT Inc., Vancouver, Canada)	Absorption peak 690 nm: avoids hemoglobin, less attenuation by blood; deeper penetration into tissues. Rapid tissue accumulation: treatment 30–150 min after infusion. Rapid clearance: skin photosensitivity lasts a few days.
5-aminolevulinic acid (ALA)	Uses heme biosynthesis to produce endogenous porphyrins (protoporphyrin IX) as photosensitizers. Absorption peak 630 nm. Rapid tissue accumulation: optimal concentration in 2–4 h. Rapid clearance: photosensitivity lasts 24 h. Preliminary data suggests may be effective for carcinoma in situ but not microinvasive cancer.
Other agents	
N-aspartyl chorine e6 (Npe6; Nippon Pharmaceuticals, Tokyo, Japan)	Bacteriochlorophyll derivatives
Polyhematoporphyrin (Photosan; SeeLab, Hamburg, Germany)	Lutetium texaphyrin (Lu-tex; Pharmacyclics Sunnyvale, CA)
Hypericin	Tin etiopurpurin (SnET2; Miravant Medical Technologies, Santa Barbara, CA)
Acridine orange	Meta-tetrahydroxyphenylchlorin (Foscan, Scotia Pharmaceuticals, Takapuna, North Shore City, NZ)
Porphycenes	Pyro-pheophoride-a methyl ester
Benzochlorins	Indocyanine green

and is probably multifactorial. Murine models suggest that endocytosis via vascular endothelium may play a role in the accumulation and retention of photosensitizers in tumors [5–8]. Other studies suggest that it may be due in part to the lipophilic nature of porphyrins. Indeed, the distribution pattern following intravenous infusion follows that of low-density lipoprotein receptors in the various organs, with the greatest amount being in the liver, followed in descending order by the adrenal glands, urinary bladder, pancreas, kidney, spleen, stomach, bone, lung, heart, muscle and brain [9]. The nature of the tumor tissue itself may be important, since the lower pH present in tumors increases the water solubility of photosensitizers. In addition, the neovascularization surrounding tumors, as well as poor lymphatic drainage, tumor angiogenesis factors and changes within tumor stromal elements, in particular tumor-associated macrophages, may further increase uptake [5,6]. Of note, many effective photosensitizers do not selectively accumulate in malignant cells per se, but rather in these tumor stromal elements.

The net result of all of these considerations is an increased tumor to tissue concentration of photosensitizer. However, this is only half of the necessary process. Once photosensitizers are concentrated within the tumor cells, they must be activated by light. It is the biophysical properties of photosensitizers, specifically the absorption spectra, which are clinically relevant here, since this determines the wavelength of light that can be used to activate them. Different wavelengths of light penetrate tissue to varying degrees, with higher wavelengths penetrating deeper. In addition, certain wavelengths may be associated with significant interference from other biologic substances, such as hemoglobin. Thus, the wavelength of light than can be used to activate a drug, as determined by its absorption spectra, impacts directly on

clinical practice by determining the effective depth of treatment [8].

In addition to the absorption spectra, the yield of singlet oxygen of different photosensitizers is another important biophysical consideration that affects clinical efficacy of PDT. The clinical action of PDT is mediated by a set of photooxidative reactions that are set in motion by the absorption of light energy, in the form of photons, by the photosensitizer. After absorbing light, the photosensitizer becomes electronically excited. The photosensitizer must be able to absorb photons of appropriate wavelengths in order to become electronically excited. The electronically excited photosensitizer transfers this energy, in the form of electrons, to molecular oxygen with generation of singlet oxygen species. This electron transfer is a type II photooxidative reaction [5,10]. Singlet oxygen can, in theory, be generated with energy as low as 0.98 MeV, equivalent to a wavelength as high as 1220 nm [11]. However, current photosensitizers can achieve efficient quantum yields of 0.2–0.6 only at much lower wavelengths, up to about 850 nm. The quantum yield is further affected by the location of the photosensitizer within the cell, with lipophilic rather than hydrophilic distributions being associated with greater efficiency. Thus, in addition to the absorption spectra of the photosensitizer, another limiting factor in terms of wavelength selection, and hence depth of treatment effect, is the effective quantum yield of different photosensitizers.

Mechanism of action

The generation of singlet oxygen begins the cascade of molecular events that lead to eventual cell death. Of note, there are multiple contributing pathways and mechanisms that play a role in PDT mediated injury, which are important to consider from a clinical perspective. These include: oxygen delivery, membrane injury, immunologic and vascular system effects and light dosimetry. Each of these factors is critical to the mechanism of action of PDT and has potential clinical implications.

Oxygen delivery to the site of PDT is pivotal since the generation of singlet oxygen is one of the initial steps in PDT mediated cellular toxicity. For PDT to be effective there must be oxygen available to facilitate a type II photoxidation reaction to generate free radicals. *In vitro*, when oxygen levels are less than 2%, tumors become resistant to PDT [12–14]. Scavengers of free radicals, such as 1,3-diphenylisobenzofuran, attenuate the generation of free radicals by singlet oxygen and reduce PDT cytotoxicity [6,13,15,16]. This is clinically relevant, since it has been suggested by some investigators that some cases of PDT failure may be due to local tumor hypoxia.

If oxygen is present in sufficient levels, then free radical generation ensues and leads to membrane damage, which is one of the basic mechanisms of cellular cytotoxicity in PDT. Because of the lipophilic nature of most photosensitizers, as measured by the water–lipid partition coefficient, the concentration of photosensitizers is greatest in the plasma membrane and mitochondrial membrane [5,17–21]. Porphyrin uptake studies demonstrate initial binding with the plasma membrane followed by extension to other internal cellular membranes [20,21]. Owing to the short lifetime and diffusion distance of singlet oxygen species, most of the damage from activation of photosensitizers occurs close to the site of localization [10]. This results in damage to plasma, mitochondrial and lysosomal membranes, leading to rapid apoptosis and an inflammatory response. Plasma membrane injury is visible immediately and is initially characterized by multiple areas of membrane injury with blebs. Larger balloon like areas form and cellular division and normal function eventually cease with subsequent cell lysis [5,17,22]. Concurrent with this injury to the plasma membrane, other cellular membranes are injured, including mitochondrial membranes, nuclear membranes, the Golgi apparatus and endoplasmic reticulum [19,23]. There is inhibition of oxidative phosphorylation and ATP generation due to mitochondrial injury, with cellular ATP levels becoming virtually undetectable 2–4 h after treatment [17,23–26].

Concurrent with this free radical induced membrane injury is a complex mixture of vascular injury, coagulation and immunologic responses. This is characterized by platelet and neutrophil activation with subsequent vascular damage, occlusion, ischemic cell death and ischemia-reperfusion injury. Part of the secondary tumor destruction that results is mediated by PDT's effect on the neovasculature of tumors. These venous derived vessels often do not have sufficient strength to

remain patent when there are high extravascular pressures. The tissue injury and edema from PDT results in decreased flow, leading to stasis, vasoconstriction, thrombosis and further interstitial edema [27,28]. Coagulation is further facilitated by injury to the vascular endothelium, with resultant agglutination and thrombus formation [29]. Studies with magnetic resonance imaging have demonstrated that vascular damage precedes actual tumor necrosis from PDT [30]. Of note, there is *in vitro* evidence that combining antiangiogenic therapy with PDT improved tumoricidal activity, although this has not yet been tested clinically [31].

Concurrent with this coagulation and vascular injury is a localized immune response. There is secondary killing of tumor cells by infiltration of activated inflammatory cells from the circulation as well as a tumor-sensitized immune reaction [10]. Antigen presenting macrophages facilitate further development of lymphoid populations with tumor-specific immunity [32–34]. These tumor-specific lymphoid cells may play a role in preventing recurrence of the PDT treated tumor.

Thus, it is a complex combination of adequate oxygen delivery, free radical generation, membrane injury, vascular injury and immune responses that leads to the clinical effects of PDT. The final factor that impacts on the effect of PDT is the method of light delivery. The entire chain of events is dependent upon accurate delivery of light. In terms of clinical efficacy, the optimum dosimetry is dependent upon four factors: the photosensitizer's characteristics and concentration at the tumor site, the light source, the rate of energy delivery (power) and the total energy delivered. We have already described how the biophysical and biochemical properties of photosensitizers impact on clinical performance characteristics.

With respect to the delivery of light, laser light is typically used because it offers the advantage of a uniform spectrum and coherence. For pulmonary applications, several lasers have received approval for clinical use. This includes continuous wavelength lasers (potassium-titanyl-phosphate [KTP] dye lasers, argon dye lasers), pulse lasers (e.g. excimer dye lasers) and less expensive diode lasers (Diomed Inc., Andover, MA). In theory, any laser could be used, provided it supplied light of the proper wavelength with sufficient precision and control of power to activate the photosensitizer.

The wavelength, power and total energy delivered, in turn, impact on how effective PDT is. Empiric data is necessary to determine the optimum power and total energy delivery for clinical applications because of the many competing considerations that are present. For instance, *in vitro* studies suggested that high dose rate would be associated with improved cytotoxicity [11,35–37]. However, conflicting *in vitro* data and some mathematical models suggested that lower dose rates might be better; *in vivo* data supported the lower dose rates as well [11,16]. The exact reason for this discrepancy is unclear, but some investigators have hypothesized that reduction of the fluence rate may increase the generation of singlet oxygen in regions of poor capillary flow. The importance of this data, however, is the observation that light dosimetry has a clinically significant impact on response and side effects. Thus, controlled and reproducible light dosimetry, the technology to deliver it and empiric evidence with clinical dose-response rates in humans is an important consideration for PDT.

Technique of PDT

The technique of PDT is a consequence of the characteristics of the photosensitizers and molecular mechanisms of action described earlier. For pulmonary applications, there are three distinct steps: delivery of the photosensitizer, subsequent activation with laser light and removal of necrotic debris. This discussion will use porfimer sodium (Photofrin; QLT Inc., Vancouver, Canada; Axcan Pharma, Birmingham, AL) to demonstrate the underlying principles relevant to clinical applications of PDT, since at the time of this writing it is the only FDA approved agent available for commercial use in the United States. However, the same underlying biochemical and biophysical concepts can be applied to evaluate the potential applications and utility of newer agents.

Delivery of the photosensitizer is accomplished through a peripheral IV infusion of porfimer sodium (Photofrin) at a dose of 2 mg/kg. After infusion, the patient is photosensitive; so instruction must be given prior to the infusion so that appropriate precautions can be taken. This includes

avoidance of direct sunlight, wearing protective clothing, large brimmed hats and the use of curtains. Indoor artificial light is no problem. Typically a handbook is given out prior to infusion with concurrent verbal instruction. The duration of skin photosensitivity varies with the agent. In the case of porfimer sodium, the duration is approximately 1 month.

Activation of the photosensitizer by light is the second element. This must be accomplished using correct dosimetry. For pulmonary applications of porfimer sodium, the wavelength is 630 nm, the power is 400 mW/cm and the total energy delivered is 200–300 J/cm. Based on the total energy delivery of 200–300 J/cm and the power of 400 mW/cm, it follows that the initial laser bronchoscopy will consist of simply placing a nonthermal laser either in or adjacent to the tumor for 500–750 s. Typically 200 J/cm would be used for carcinoma in situ (CIS) or for smaller airway tumors; up to 300 J/cm would be used for more advanced disease in large airways.

Light is delivered via laser fibers passed through the instrument channel of the bronchoscope. The laser fiber used can be tailored to fit the clinical situation. A microlens is often best for small superficial bronchial tumors that are end-on to the bronchoscope while a cylindrical light diffusing fiber is often useful for applications in which the tumor is parallel to the bronchoscope and is either nodular or polypoid in nature. The cylindrical light diffusing fiber can be used in two ways. The fiber can be inserted directly into endobronchial tumors (interstitial delivery) or placed alongside the tumor in the bronchi.

It is important to recognize that the type of fiber used may affect dosimetry and hence efficacy [38]. The dosimetry of forward projecting fibers or bulbous tip spherical distribution fibers is dependent upon certain assumptions that may or may not hold true. For example, when using a forward projecting fiber, the power output per square centimeter is dependent upon the area illuminated. For a fixed power output, the power per square centimeter will decrease as the area illuminated increases. If the forward projecting fiber is close to the tumor, a smaller area is illuminated. In this situation, a higher power per square centimeter would result. Estimating the distance to a tumor and measurement of the area illuminated by a forward projecting fiber is difficult in the airway. Maintaining this distance for the duration of a procedure is even more difficult. This results in variable power delivery per square centimeter. Thus, control of dosimetry may be adversely affected. For this reason, we generally prefer to use cylindrical light diffusing fibers for pulmonary applications of PDT. For bronchoscopic applications, the 1 cm and 2.5 cm fibers are the most useful commercially available fibers.

Following activation of the photosensitizer by laser light, tumor necrosis occurs as a consequence of the generation of singlet oxygen species, free radical mediated membrane injury, vascular injury and immune responses. This usually takes place over the course of 24–48 h. This necessitates that a third step be taken, namely the removal of necrotic debris, since there will be obstruction of the airway. Repeat bronchoscopy is warranted at this point for pulmonary hygiene and this is usually done 24–48 h after the initial bronchoscopy. At this stage the tumor is very avascular and will have the consistency of extremely thick mucus and will appear white, presuming that PDT was successful. As predicted based upon the mechanisms of injury discussed earlier, bleeding with mechanical debridement will be minimal. Removal of debris can be achieved with bronchoalveolar lavage and mechanical resection. This is also greatly facilitated by the use of cryotherapy, which allows rapid removal of the large plugs of necrotic tissue that are generated by PDT. Aggressive debridement is critical since this debris can lead to atelectasis and respiratory compromise. After the removal of debris, if residual tumor is present, a second laser treatment to generate additional photosensitizer activation can be performed, since the photosensitizer will be present at adequate tissue levels for a prolonged period of time. However, if an additional laser treatment is given, repeat pulmonary hygiene bronchoscopy is mandatory 24–48 h later. Pulmonary hygiene bronchoscopies should be repeated until there is no additional debris being generated by the PDT.

Other than airway compromise from necrotic debris, the only other common side effect of PDT is photosensitivity. This consists predominantly of a sunburn type reaction that is easily avoided with careful patient instruction. Delayed bleeding from

tumors is a rare but significant possibility, especially if a tumor invading a major blood vessel is treated. Because of this, it is wise to assess the extent of tumor invasion and blood vessel involvement with computed topography (CT) imaging prior to PDT. Finally, any infection resulting from post-obstructive pneumonia due to necrotic debris needs to be treated aggressively with a combination of antibiotics and removal of the obstructing lesion.

Clinical applications and evidence base

Clinical applications of PDT can be divided into two distinct categories: treatment of early stage lung cancer and palliative treatment of malignant airway obstruction. Early stage disease in this case refers to CIS and early superficial bronchial cancers that are potentially curable. Palliative treatment of malignant airway obstruction constitutes all cases with unresectable tumor, either primary or metastatic, that obstruct the central airways, including the trachea, mainstem bronchi and bronchus intermedius.

Early stage lung cancer and CIS

The noninvasive nature of PDT, its relatively selective tumor destruction, preservation of lung parenchyma and the ability to repeat treatments makes it a potentially ideal method for treating CIS. When determining how best to use PDT for CIS, it is important to consider several factors, including patient and lesion selection criteria, variations in the definition of early stage lung cancer used in the literature and case finding methods.

The pivotal clinical issue is what criteria or tests can be used to guide proper patient and lesion selection for PDT treatment among those patients with *possibly curable* CIS or early stage lung cancer. This question requires us to have a clear and precise idea of what constitutes early superficial bronchial carcinoma potentially curable by PDT and what constitutes stage IA disease in which PDT is unlikely to result in long-term response.

As PDT is a local treatment, it cannot address metastatic disease to the lymph nodes or other organs. Thus, any lesion with peribronchial spread or lymph node involvement cannot be considered amenable to treatment with PDT for cure. The risk of lymph node involvement increases with the size of the lesion [39]. A good rule of thumb is that optimal lesions for PDT are those that are less than 1 cm in length. The risk of lymph node involvement increases once the length exceeds 1 cm; at 1–3 cm it increases to 23%, and at greater than 3 cm in length the risk increases to 67%. Thus, length of the lesions, as a predictor of occult nodal involvement, is one criterion for lesion selection.

In addition, as described earlier, the wavelength of light dictates the maximum effective depth of PDT treatment. For porfimer sodium, this is about 3–5 mm. One consequence of this is that PDT can also only provide curative treatment for lesions that have not invaded beyond the cartilaginous layer of the bronchial wall [40–42]. However, assessing the depth of invasion is difficult with standard bronchoscopy and radiographic imaging. While size of the lesion correlates with depth of penetration, the correlation is not precise enough.

The availability of endobronchial ultrasound (EBUS) offers the potential to greatly improve patient selection and hence long-term response rates, since it is very effective in assessing depth of invasion. In a pivotal study by Miyazu *et al.*, of 18 biopsy proven early stage lesions less than 2 cm in diameter that were thought to be appropriate for PDT with curatives intent, 9 were found to have evidence of extra-cartilaginous extension of tumor by EBUS [43]. Of these 9 patients with extra-cartilaginous extension by EBUS 6 eventually underwent surgical resection, and in all cases extension beyond the cartilaginous layer was verified by pathology. The nine patients in this study without evidence of extra-cartilaginous extension by EBUS were treated with PDT, and all had a complete response without evidence of disease recurrence at a median follow-up of 32 months. Of note, diameter of the lesion did not predict depth of tumor invasion with sufficient precision to be clinically useful. While all 4 of the lesions that were greater than 1 cm in diameter had extra-cartilaginous spread, among the other 14 lesions less than 1 cm in diameter, 5 were found to have extra-cartilaginous extension.

Based on this, it is clear that one limitation of PDT for the treatment of early stage lung cancer, namely that of proper patient selection, can be addressed by combining EBUS with PDT.

Table 9.2 PDT in early stage lung cancer.

First author (Ref.)	*Tumors (n)*	*Clinical stage and indication*	*Complete response* (%)*	*Recurrence (%)*
Ono [45]	39	CIS and IA	31	33
Edell [46]	14	IA	93	21
Kato [47]	95	CIS and IA	83	6
Furuse [39]	59	CIS and IA	85	10
Sutedja [44]	39	CIS (17) and IA (22)	100 versus 50	29
Sutedja [50]	26	Stage I (11) and III (15)	91 versus 0	NR
Patelli [49]	26	Early stage	62	6

*Definition of complete response varied by study; CIS, carcinoma in situ; NR, not reported or not applicable.

This is particularly important when reviewing the literature and the evidence basis for the use of PDT in early lung cancer. Early trials with PDT did not have the benefit of EBUS technology to guide patient selection, and as a result response rates were probably suboptimal. It is also important to recognize that the definition of early stage lung cancer varies significantly between trials. Indeed, many studies of PDT in early stage lung cancer actually enrolled both patients with true CIS and patients with stage IA disease (Table 9.2). The patients with stage IA disease often had either declined surgery or were felt to be non-surgical candidates because of medical comorbidities. These patients would be expected to have a higher rate of recurrence than patients with true CIS [44]. The response rates reported by these studies for the aggregate populations would therefore be falsely low if extrapolated to true CIS patients. From an epidemiology perspective, this is a question of the external validity of the trials – the results are true, but the aggregate probabilities of response that are reported are not necessarily applicable to patients with true CIS. Given this problem in defining early stage disease in older trials, as well as their lack of EBUS guidance, it seems probable that the aggregate long-term response rate in carefully selected patients, using EBUS, should exceed the 21–75% rate reported in the literature for prior trials of PDT [45–53].

However, while some of the major obstacles to PDT treatment of early stage disease have been overcome, some other major issues remain to be resolved if PDT for early stage lung cancer is to reach the next level. Specifically, the method of case finding and the clinical context in which PDT is used is important to consider. Autofluorescence bronchoscopy has been advocated as one potential means of identifying patients with early stage lung cancer that may be amenable to treatment with PDT. While this research is promising, to date there has been no definitive large scale clinical trial demonstrating that autofluorescence bronchoscopy, combined with PDT and EBUS or other technologies, can be used in a cost-effective manner to both find and treat early stage lung cancer. Thus, from the public health perspective, any evaluation of PDT for early stage lung cancer must take into account not only the method and efficacy of treatment, but also the efficiency of the case-finding methodology that is utilized.

Treatment of malignant airway obstruction

While PDT for early stage lung cancer represents an opportunity to make a large impact on lung cancer mortality, the population of patients eligible for treatment remains small due to problems with case finding as described earlier. The majority of patients with lung cancer today have advanced disease that is not resectable. Many of these patients will develop malignant airway obstruction. Because of this, at the present time, there is a far greater need for palliative treatments of patients with malignant airway obstruction than there is for treatment of CIS.

Malignant airway obstruction can be caused by either extrinsic compression of the central airways or intraluminal obstruction by tumor. Extrinsic compression is best treated with airway stenting and this is addressed in other chapters. Intraluminal

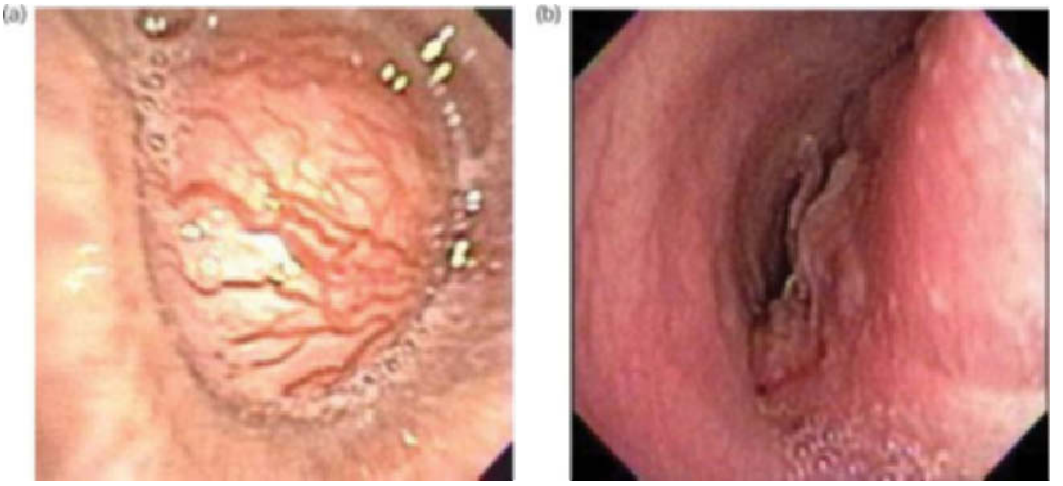

Figure 9.1 (a) Advanced malignant airway obstruction with intraluminal non-small cell carcinoma of the left mainstem bronchus. This lesion is suitable for intervention with photodynamic therapy (PDT). (b) Malignant airway obstruction due to extrinsic compression of the trachea. This is not suitable for PDT. Airway stenting would be a consideration.

obstruction, also called endobronchial obstruction, is best treated with ablative therapies that destroy the tumor directly (Figure 9.1). There are a variety of bronchoscopic ablative therapies available for treatment of advanced malignant airway obstruction, including Nd:YAG laser, brachytherapy, cryotherapy, electrocautery and PDT.

The general technique of PDT when applied to advanced malignant airway obstruction is the same as it is for early stage disease. However, there are some special considerations that warrant emphasis in patients with advanced malignant airway obstruction. First, the total energy delivered and the number of treatments varies by indication. For CIS, 200 J/cm with one light application will typically be needed. In contrast, for patients with advanced malignant airway obstruction, anywhere from 200 to 300 J/cm will be needed, often with repeated treatments, since there frequently is residual tumor visualized after the initial necrotic debris is removed. In addition, unlike Nd:YAG laser, PDT takes time to have an effect. The tumor necrosis that takes place during the 24–48 h following laser light application and drug activation can cause significant mucus plugging, atelectasis and airway compromise that may temporarily worsen the patient's condition. Since the amount of tissue necrosis is greater in those with advanced disease as compared to those with early disease, the amount of atelectasis and airway compromise is also more pronounced. Indeed, acute respiratory failure secondary to mucus plugging of the large airways has been reported with PDT, especially when there has been treatment within the trachea [10, 54].

Unfortunately, there are few randomized controlled trials comparing PDT with other modalities and no studies comparing PDT with a true placebo arm [10,12,55]. As such, the body of evidence consists primarily of observational case series data and a few small, randomized trials comparing PDT with Nd:YAG laser. Outcome measures vary between studies and are not standardized, further limiting the ability to compare the results of PDT with other modalities. Given these limitations, we can still draw some useful conclusions regarding the clinical efficacy and performance characteristics of PDT for malignant airway obstruction.

The case series data indicates that PDT, when used for palliation of advanced malignant large airway obstruction in carefully selected patients, is safe and has comparable efficacy to other modalities, including Nd:YAG laser. In a large prospective series of 100 patients with advanced inoperable stage IIIA–IV bronchogenic cancer with endobronchial obstruction, PDT resulted in significant improvement in terms of endobronchial obstruction, FEV1, FVC and palliation of symptoms [56]. In another

Table 9.3 PDT in advanced malignant airway obstruction.

References	*Tumors (n)*	*Stage*	*Response*
Moghissi [55]	26	Advanced	Obstruction at 1 month: 39.1% Nd:YAG versus 16% PDT
Dougherty [10]	211	Advanced	Response rate at 1 month:
			Europe: 36% Nd:YAG versus 61% PDT
			United States: 19% Nd:YAG versus 42% PDT
Diaz-Jimenez [12]	31	I–IV	Time to failure 38 days Nd:YAG versus 50 days PDT
			Response at 1 month: 23.5% Nd:YAG versus 38.5% PDT

series of patients with advanced primary lung cancer, the mean luminal obstruction fell from 84 to 18% 4 weeks after PDT [57]. Importantly, PDT can be done with either the flexible or rigid bronchoscope.

When combined with other modalities as part of a multi-modality approach, PDT has been shown to be of benefit as well. In a study by Lam *et al.* of PDT combined with radiotherapy (RT) versus RT alone for patients with advanced endobronchial obstruction, PDT + RT was significantly better than RT alone in terms of airway reopening (70 versus 10%) [58].

In the few trials that have compared PDT directly with Nd:YAG laser prospectively, efficacy has been similar to that of Nd:YAG (Table 9.3). Moghissi *et al.* demonstrated that the use of PDT in stage III inoperable lung cancer resulted in a greater improvement in FEV_{-1}, FVC, and median percentage obstruction after 1 month [55]. Other investigators have also reported slightly greater improvements with PDT as compared to Nd:YAG laser with long-term follow-up [10,12]. It may be that this improvement in duration of response is secondary to destruction of invisible submucosal tumor that is missed with the Nd:YAG laser or it may be due to the secondary vascular and immune responses that PDT induces [32–34]. Side effects in these trials were significant but comparable to that of other interventions. The primary risks reported were skin photosensitivity, atelectasis with respiratory compromise and delayed bleeding from tumor.

The advantages of PDT in terms of duration of response, ease of use and safety need to be weighed against the limitations of PDT. Careful patient selection is crucial. PDT is also quite expensive, with the photosensitizer alone frequently being in the range of $5000 per patient. Thus cost-effectiveness needs to be considered as well. On balance, it seems reasonable to avoid the use of PDT if possible when there is tracheal involvement or when the patient lacks sufficient ventilatory reserve to tolerate the atelectasis and mucus plugging that may ensue. In addition, when rapid reopening of the airway is needed, PDT is probably not the best choice, since it does take several days to reestablish an optimum airway. Other alternatives, such as Nd:YAG laser or electrocautery, should be considered in these cases. In those patients with stable respiratory function and sufficient ventilatory reserve, PDT is a viable consideration and may offer some modest benefits.

Summary

Photodynamic therapy uses photosensitizing agents that are inactive until activated by light of a particular wavelength. The biochemical and biophysical properties of the photosensitizer, especially the absorption spectra and quantum yield of singlet oxygen, determine the wavelength(s) of light that can be used to activate them. The wavelength of light in turn determines the depth of tissue penetration and also the effective treatment depth for PDT. Following intravenous infusion, these agents are selectively retained and concentrated in tumors and their stromal elements. When activated by light of the proper wavelength, singlet oxygen species and free radicals are generated, resulting in membrane injury, vascular damage and a potent immune response leading to tumor necrosis. For PDT to be effective in early stage disease there must be no spread to regional lymph nodes and the depth of invasion must not extend beyond the cartilage layer. Bronchoscopic inspection to determine depth

of invasion is imprecise, and EBUS should therefore be used to improve patient selection. Lesions that are less than 1 cm in diameter without evidence of extra-cartilaginous spread by EBUS are optimal for PDT. PDT can also be used for palliation of intraluminal malignant airway obstruction. It offers the benefits of a good duration of response and ease of use. These benefits must be balanced against the slow onset of action and the potential for atelectasis and airway obstruction from necrotic debris. When used for advanced disease, it should be integrated into a multi-modality approach with other interventional bronchoscopy tools, as well as chemotherapy and radiation.

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10 CHAPTER 10

Stenting of the tracheobronchial tree

Armin Ernst, MD

Introduction

Stenting of the airways may be performed for a variety of airway disorders, including intrinsic and extrinsic compression, fistula formation and hyperdynamic obstruction. Stents have even been used as a delivery vehicle for other therapeutic approaches such as gene therapy. Stenting has become an integral part of the armamentarium for therapeutic endoscopy. This chapter will discuss current indications for airway stenting, highlight problems and controversies and also address technical issues related to the placement of airway stents.

Early reports of stent placement into the airways date back to the beginning of the century, but due to inadequate materials and equipment, it has only had very limited applications. The first stent that has found widespread use was the "T"-tube, or Montgomery Stent, introduced in 1962 for the treatment of subglottic stenosis. A further advance was the introduction of a dedicated indwelling silicone tube stent in 1989 by Dumon in France. With the report on the use of this particular device, we commonly associate the start of the modern era of airway stenting. The Dumon stent to date represents the gold standard for airway stent application in regards of their safety, ease of application and outcome. Metal stents have also been in use since the mid-1980s. Unfortunately, the initial reported outcomes in patients were sometimes disastrous. The underlying reason has been inappropriate physical characteristics of the particular stent designs, as they were primarily intended for use in the biliary tree and vascular system. The last decade has seen numerous new stent designs in the use of metal alloys and stent architecture. Since then the safety record of metal stents placed into the airways seems to have vastly improved.

The question frequently arises as to whether metal or silicone stents are superior in regards to safety and efficacy. Unfortunately, to date no stent design presents an optimal solution for all indications and problems encountered. Therefore, the stent type should be chosen according to a patient's specific problem and situation. This should be the overriding principle, not what an operator can and cannot do. New stent designs combining properties of both types and bio-absorbable stents as well as other innovations are on the horizon and may make the discussion and need for choice less problematic in the future.

Indications for airway stents are listed in Table 10.1. In general, if stenting is used for airway obstruction, a multimodality approach to establish maximal airway patency is preferred. Before a stent is introduced, intrinsic airway obstruction

Table 10.1 Current indications for airway stents.

Extrinsic obstruction
Malignant intrinsic obstruction after airway patency has been reestablished
Airway fistula
Benign intrinsic stenosis after dilation or other resection*
Tracheomalacia in select cases*
Airway stabilization after airway surgery (temporary)*

*Removable stents preferred.

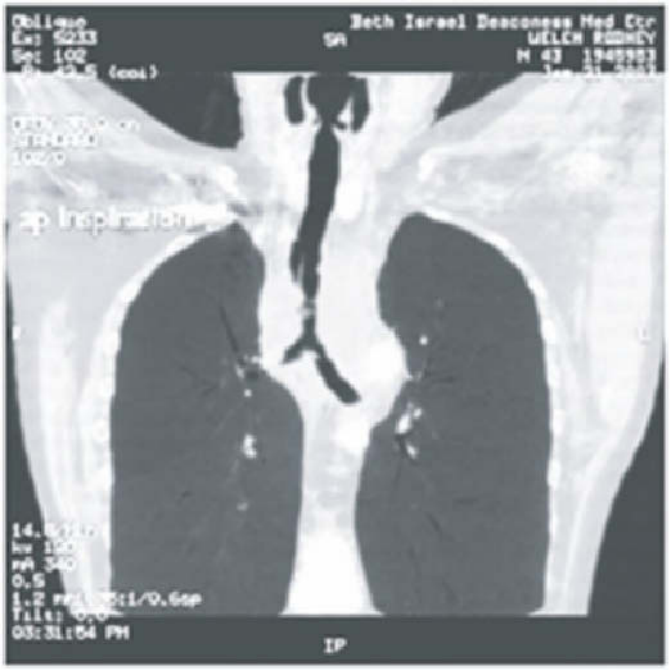

Figure 10.1 Example of an airway computed tomography (CT) reconstruction. Shown is an extensive tumor mass invading the distal trachea and both mainstems with high-grade obstruction. Distal patency bilaterally is demonstrated. The CT allows for appropriate preparation of the procedure in this high risk individual as well as exact stent sizing. Specialized software and multidetector CT scanners are necessary for high-quality images.

should be relieved and airway patency reestablished as closely as possible in diameter to the normal lumen size. This can be achieved by mechanical resection, dilation, thermal resection, photodynamic therapy, radiation or other means. Details of those modalities are discussed elsewhere in this book. In malignant airway obstruction, it remains a topic of discussion, if establishing an airway lumen should immediately be followed by stent placement, or if stenting should be done in case of recurrence or other treatment failure later in the course. A leading cause for the discussion is the cost associated with airway stenting and the issue remains unresolved to date.

In order for stents (or any other measure to relieve an obstruction) to be effective, airways distal to the obstruction need to be patent. We therefore perform careful endoscopic, endobronchial ultrasound (EBUS) and non-endoscopic evaluation prior to any airway intervention (Figure 10.1). Additionally, it may be necessary to ensure that perfusion of the obstructed lung is not compromised to a nonreversible degree, in order to avoid post-procedure Ventilation Perfusion (V/Q) mismatch and worsened clinical status of the patient. Airway stents are most effective when placed into large central airways. Lobar orifices only rarely are stentable or leave a patient with good results.

Airway fistulas are often associated with significant morbidity and premature mortality, especially in the case of malignant fistulas. Stenting with the goal of sealing the communicating tract has significantly changed the quality of life and survival for patients with malignant tracheoesophageal fistulas (TEF). We generally prefer concurrent stenting of the esophagus and the airway for maximum effect and survival benefit. Stenting in case of a TEF can be challenging and a possibility of worsening the fistula accidentally exists in less experienced hands.

Stenting for hyperdynamic airway obstruction (tracheomalacia) is occasionally indicated. Details of the treatment of tracheomalacia are provided in a different chapter. As with any benign disorder, stenting of the airways is a difficult problem. As a rule, we only recommend the use of silicone stents whenever possible. This rule will ensure that surgical treatment options for the underlying disorder are not jeopardized and that stents can easily be removed in case of problems.

Sizing and choice of the stent may be difficult. Length and diameter can be measured during bronchoscopy, or an airway computed tomography (CT) with reconstruction may be useful (Figure 10.1). Stents need to be long enough to cover the area in question and extend 5 mm proximally and distally and should fit snuggly in diameter. Stents that are chosen too small will migrate and those chosen too large in diameter may exhibit excessive forces on the airway wall with associated granulation and possible necrosis. EBUS may be beneficial to exactly demonstrate the extent and length of tumor involvement even in the submucosa of the airways. Studies show that use of EBUS may change the chosen stent length. Commonly used sizes are 10–14 mm in diameter for mainstem bronchi with 2–4 cm in length. Tracheal sizes frequently fall into the range of 14–18 mm in diameter with 4–8 cm length. The left mainstem is often more easily stented than the right, as the right upper lobe should not be covered, if still patent.

When choosing a particular stent type, several characteristics should be kept in mind. Silicone stents require rigid bronchoscopy for placement. Rigid bronchoscopy is most commonly performed in an operating room under general anesthesia and as such access for pulmonologists can be limited. The distinct advantage of rigid bronchoscopy is the ease and speed with which even difficult procedures can be performed safely. It also provides a safe way of working in the airways of patients with an unstable respiratory status and allows for prolonged procedures to be performed comfortably and safely. Silicone stents are easily removed even after long periods of time and have a good track record. They do not conform to changes in airway diameters in the diseased airway and tend to migrate more frequently than metal stents. Silicone stents can be custom made in different shapes, but the inner to outer diameter ratio in conventional silicon stents limits their use in smaller airways and in children.

Metal stents may be placed with the flexible bronchoscope. They adjust to varying airway diameters and shapes and have a favorable inner-to-outer diameter ratio compared with silicone stents. They rarely migrate, but fatigue fractures and formation of granulation tissue are of concern. Removal after 6–8 weeks can be difficult or impossible. It is for that reason that the use of metal stents in benign disease should be limited to experienced centers. Metal stents frequently are available with or without coating. When used for intrinsic malignancies or airway fistula, a covered stent should be used. If the compression is purely extrinsic, a uncovered stent may suffice.

The accomplished interventionalist should be capable of placing both silicone and metal stents and be able to make individual choices in the best interests of the patient.

Carinal abnormalities or obstructions near the carina may be difficult to treat with tube stents and frequently a "Y"-shaped stent is the more satisfying solution. Alternatively, multiple metal stents can be placed into the proximal end of both right and left main bronchus and distal trachea formulating a "Y" stent *in vivo*. This alternative approach is expensive and provides inferior coverage of the carina.

Patients with benign airway disorders present a difficult population when stenting is considered. Due to the inherent complications associated with airway stents, the indications have to be strict. It is imperative to objectively document symptomatic improvement with the use of an endoprosthesis. It is our practice to perform a pre-procedural functional assessment including pulmonary function tests and an exercise assessment such as a 6-min walk test. After the stent has been placed, we repeat these tests. If there is no objective improvement, the stent is removed. As metal stents may not be removable after several weeks, experts are divided on the safety in their use for benign disease. As newer surgical technologies are becoming available to approach even malacic conditions, the overriding principle in airway stenting for benign disorders has to be not to perform any procedures that may cause harm and may exclude a patient from curative surgery.

Silicone stents

Most commonly used is the Dumon stent (Figure 10.2), but other models are available, e.g. the Hood stent or the screw thread stent, developed by Noppen. The chosen stent is loaded into the distal opening of the rigid introducer tube either by a dedicated device or by folding it and pushing it into the tube. The diameter of the ventilating

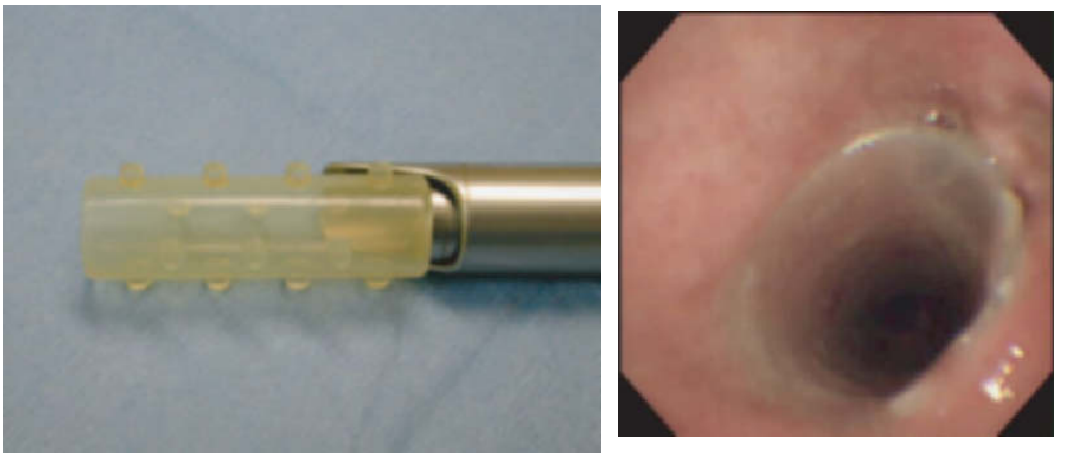

Figure 10.2 Example of a Dumon silicone stent. Depicted to the left is a stent at the tip of a rigid bronchoscope, to the right a stent *in vivo*. Observe the snug fit in the airway.

scope has to be chosen according to the stent size. Some systems are color coded to allow for optimal matching of the introducer tube and bronchoscope diameter. The introducer with the stent inside is passed into the stenotic area. The stent may either be pushed out with the introducer plunger or with the help of forceps while the bronchoscope is slowly withdrawn. The stent will unfold in the airway once released. If the stent is too proximal, it may be gently pushed with the tip of the rigid bronchoscope and if it is deployed too distally, it can be pulled back with the help of forceps. A properly sized stent will fit snugly into the airway when completely unfolded (Figure 10.2). External studs or protrusions outside the stent are designed to minimize migration risk.

Montgomery T-tubes are designed for use in subglottic or high tracheal obstructions. They are available in different diameters and their proximal and distal length can be cut to fit the patient's specific requirements. Care must be taken to leave enough distance to the vocal cords to ensure a good voice. The stent is placed through a tracheal stoma leading with the distal end toward the carina. When the distal and proximal ends are advanced into the trachea, gentle traction is applied to the external limb to allow the stent to straighten out. Minor adjustment may be made with the help of the rigid bronchoscope. The stent is easily removable through the stoma by gentle pull and should generally be capped to allow for a good voice and minimize secretion build-up. Suctioning and stent care can be performed through the external limb.

"Y"-stents such as the Freitag or dynamic stent require a skilled endoscopist to be placed successfully (Figure 10.3). These stents cannot be loaded into a rigid bronchoscope. Special introduction forceps are available to place the stent through the vocal cords into the trachea with a laryngoscope providing visualization. We often perform direct suspension laryngoscopy to expose the vocal cords and provide ventilation. The stent is then advanced with the forceps through the cords and placed into the trachea. This is followed by rigid bronchoscopy to assure proper placement and to allow for necessary adjustments.

Metal stents

Most experts agree that older stents such as the Gianturco stent no longer have a place in the treatment of airway disorders. An exception to this rule is at times still the Palmaz stent. This stent is hardly used anymore in adult airway disorders, as its design allows the stent to crush and not re-expand with coughing. It is still in occasional use in the pediatric population, as it is currently the only commercially available stent in small enough sizes. This discussion will focus on newer generation models.

In adult applications, most metal stents used now are made from metal alloys (such as nickel and titanium, or nitinol), which are self-expanding

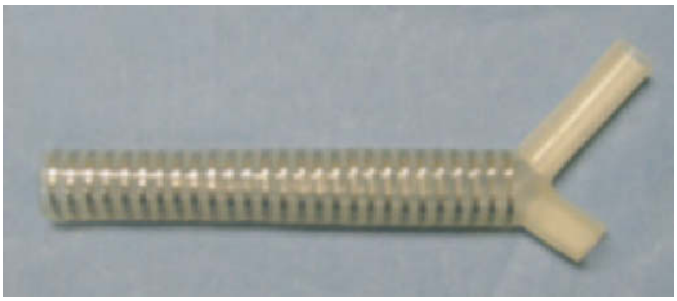

Figure 10.3 Example of a Freitag dynamic stent. The stent is available in different diameters. The length of the tracheal and mainstem segments can be cut to suit individual needs.

and possess a "shape memory," which allows them to resume their original shape after having been compressed.

Metal stents are commonly placed with the flexible bronchoscope under conscious sedation or with rigid bronchoscopy. In the unstable patient or when working in a single airway, the use of an endotracheal tube or laryngeal mask airway under general anesthesia by flexible bronchoscope or even better the use of a rigid open ventilating scope are the safer choice. Metal stents are generally available covered or uncovered. Membrane-covered stents are intended to be used to prevent tumor growth into the lumen of the stent in malignant stenosis and to seal openings in patients with airway fistula.

Generally, stents are secured onto an introduction catheter and held in place either with a sheath or other removable system (Figure 10.4). A guidewire is placed into the airway past the lesion. The catheter is then advanced over the guidewire into the airway until the stent is in the desired location (Figure 10.5). This can easily be performed visually, but especially for the novice, fluoroscopy can be performed to adjust the stent placement. Once the location is satisfactory, removing the sheath or pulling a string will release the stent to the preset diameter and deploys the stent. It is important to remember that it is safe to choose the stent slightly too big, but incomplete expansion will cause some models to be longer than they would have been if completely expanded. Metal stents are easy to pull back for adjustment. Pushing a stent down is more difficult. Thus, in case of uncertainty, it is preferable to deploy somewhat too distal and pull the stent back, if needed. Stents usually take 24–48 h to reach their maximum diameter and may be dilated from the inside with balloon dilators.

Figure 10.4 Example of a covered metal stent. Shown is the partially deployed stent device and the sheath constraint system.

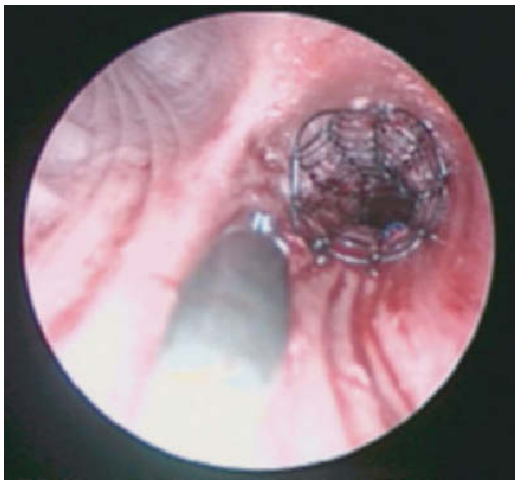

Figure 10.5 Example of a uncovered airway stent placed into the right mainstem for post-lung transplant stenosis.

Once a stent has been placed, follow-up needs to be arranged. In the case of metal stents, we perform bronchoscopy within 6 weeks. This allows for necessary adjustments, as most stents are not yet embedded. Specific follow-up schedules differ between centers and airway CTs are becoming increasingly popular (but are not yet validated), as they are noninvasive.

Pre-procedural steroids and antibiotics have no proven value and should be avoided. All patients with airway stents should carry a card identifying the type, size and location, together with contact numbers for the center that placed the stent. A medical alert bracelet may also be helpful. In case of tracheal stents patients need to be informed that the device is not a contraindication to intubation. Most tracheal stents can be intubated, but it may require flexible bronchoscopic guidance and should be performed by an experienced anesthesiologist or endoscopist.

Granulation formation may lead to recurrent obstruction within a stent or at its ends. Other problems include migration, breakage and infection. In case of granulation tissue requiring endoscopic intervention we recommend the following. If a silicone stent is in place, it can easily be removed and the granulation tissue can be removed by any means safely. Metal stents can rarely be removed for this purpose and treatment of granulation tissue is therefore more complex. Electrocautery and argon plasma coagulation (APC) as well as laser therapy have all been used successfully in experienced hands. Cryotherapy may also be used without any significant danger. Other, less well-studied approaches include the application of topical mitomycin C, brachytherapy and photodynamic therapy. If metallic stents are severely compromising the airway, removal with all its associated complications may be necessary.

Even though there have been significant improvements in stent design over the last 10 years, more advances will be seen in the near future. Hybrid stents that are made from silicone, but are compressible like metal stents are available. Metal wall stents without exposed wires are currently undergoing testing. Other concepts include stents made from bio-absorbable materials and materials impregnated with radioactive or chemotherapeutic compounds.

As with most complex airway procedures, airway stenting should be performed in a center experienced in this therapy, which has all necessary technology available.

Suggested reading

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11 CHAPTER 11

Transtracheal oxygen and percutaneous tracheotomy

David Feller-Kopman, MD

Transtracheal oxygen

Introduction

Since the landmark Nocturnal Oxygen Therapy Trial was published in 1980 [1], it has been clear that the continuous use of supplemental oxygen is critical in prolonging the life of patients with chronic obstructive pulmonary disease (COPD) and hypoxemia. Most commonly, oxygen is delivered via a nasal cannula (NC), and there are currently approximately 800 000 patients in the United States receiving supplemental oxygen [2,3]. Unfortunately, oxygen delivery systems can be cumbersome. In addition to the length of the oxygen tubing, large oxygen cylinders often pose limits on patient's mobility. Although lighter-weight portable sources, as well as oxygen-conserving devices such as reservoirs, and intermittent-flow designs have been developed, patients can only typically leave the house for up to 7 h if using higher flow rates. Additionally, when delivered via NC, irritation of the nasal mucosa and the skin on the upper lip and ears can develop. There may also be a real, or perceived, social stigmata toward having "everyone know" that an individual requires the use of oxygen. The compliance with prescribed oxygen is typically poor.

In 1982, Heimlich described a method of delivering oxygen directly into the trachea [4]. Since that time, there have been numerous studies associating transtracheal oxygen (TTO) delivery with decreased oxygen flow rates [4–12] leading to decreased oxygen costs [4], improved patient compliance, [5,6] decreased frequency of hospitalization [4,6,7] and improved exercise tolerance [6]. There have also been numerous case reports of complications, [4–7,10,11,13] several of which describe life-threatening tracheal obstruction from the formation of mucus balls at the catheter tip. This chapter will review the most relevant literature as well as describe the technique of TTO catheter placement.

Transtracheal catheters

Dr. Henry Heimlich was the first to investigate the use of a 16-gauge Teflon catheter inserted through the trachea to assist rehabilitation in patients with chronic lung disease [4]. He rationalized that nasal oxygen delivery is largely wasted. All oxygen delivered during exhalation is lost to the atmosphere, and during inhalation, a substantial amount of the delivered oxygen is wasted as dead-space ventilation. This often results in the need to use flow rates of 2–4 L/min. Heimlich believed that by bypassing the oro- and nasopharynx, lower flow rates could achieve the same clinical benefits. He further postulated that the respiratory muscles are at a mechanical disadvantage with nasal, as compared to TTO, and that delivering oxygen directly into the trachea will lower the work of breathing [4,5]. Initial experiments in 4 dogs suggested that the PaO_2 could be maintained with four times less FiO_2 when it was delivered to the distal trachea rather than more proximally in the trachea. His subsequent investigation in 14 patients with chronic lung disease, including 9 with emphysema and 5 with coal pneumoconiosis showed significant reductions in the flow rate required to achieve

improved oxygenation. Pre-catheter placement, mean PaO_2 was 52 mmHg (SpO_2 83%) on room-air and 77 mmHg (SpO_2 94%) on 2 L/min via NC. Mean PaO_2 after TTO catheter placement was 73 mmHg (SpO_2 94%) with a flow rate of only 0.5 L/min. His patients also reported subjective improvements in quality of life [4,14].

In 1986, Christopher and colleagues introduced, via the Seldinger technique, a larger, 8 F (2.7 mm) diameter catheter for the purpose of delivering higher flow rates for patients with refractory hypoxemia [7]. They found that this group of patients required more than 3 L/min to achieve adequate oxygenation, and the 16-GA catheter used by Heimlich created too much back pressure on the system causing oxygen loss at the pop-off valve. Eight patients with severe and refractory hypoxemia (polycythemia, and $PaO_2 < 50$ mmHg despite up to 8 L/min NC oxygen) received the new TTO catheter, with a mean 50% increase in PaO_2 and 72% reduction in flow rates [7].

Cook Critical Care developed a transtracheal catheter that is implanted surgically, typically under general anesthesia, and tunneled with the exit point over the upper abdomen; however, the catheter has been discontinued and is no longer available for clinical use [15–17]. The intra-tracheal portion of the catheter is much shorter, compared to the SCOOP catheter (designed by Transtracheal systems, Denver, Colorado, discussed later). One potential advantage of the tunneled catheter was that it is even more conspicuous than the SCOOP [18]. In a study of 10 patients using the tunneled catheter, Jackson and colleagues found it to be well tolerated, and associated with a 40% reduction in oxygen savings [17].

Spofford and Christopher's group went on to manufacture a kit (SCOOP, Transtracheal Systems), and describe a program for TTO delivery [10]. Currently, Transtracheal Systems is the only manufacturer of TTO catheters. They have compiled several resources for patient education and procedural instruction, all of which can be found on their website (www.tto2.com) and Christopher has also recently published an extensive review detailing the procedure [19].

The actual design of the best catheter has also been subject to investigation. Heimlich believes that the narrowest catheter able to provide sufficient flow should be used, and that it should have only one distal opening [5]. He suggests that the lack of side ports prevents the introduction of mucus, and therefore the need to remove the catheter for cleaning. Additionally, by creating a penetrating jet of gas, the resultant turbulent flow and bi-directional convective gas streaming serves to aid in gas mixing that is normally achieved by the ventilatory muscles. In a study of 200 patients with chronic lung disease, Heimlich and Carr investigated the use of the micro-trach, a single lumen 1.7-mm (5 F) catheter to deliver TTO. The procedural and overall complication rates were negligible; there were three episodes of portions of the catheters breaking and being expectorated. Over the seven-year follow-up, 17% of patients elected to return to NC oxygen – the details leading to this decision were not reported [14]. Walsh has also reported cases of catheter fracture, though only occurring in 9 patients over a course of 595 patient–months follow-up.

Patient selection and procedural guidelines

As with any procedure, patient selection is crucial, especially early in one's experience. Obviously, TTO placement is being performed in patients with compromised pulmonary function. The ideal patient should be hypoxemic as defined by the Medicare guidelines for oxygen reimbursement: an arterial blood gas obtained on room air should show PaO_2 less than 55 mmHg, or a PaO_2 of 56–59 mmHg if the patient also has (a) dependent edema caused by congestive heart failure, (b) "P" pulmonale on electro-kareliogian (EKG) (P wave greater than 3 mm in leads II, III or AVF) or (c) a hematocrit more than 55%. Room air oximetry may also be used to document the need for oxygen if the SaO_2 is less than 85% or if, 1, 2 or 3 is present with a SpO_2 of 86–89%. Contraindications to TTO placement include uncooperative/noncompliant patients, patients who can not comprehend the care instructions or are too anxious to participate in the care required for the catheter and patients who have herniation of the pleura under the puncture site. Transtracheal systems also recommend performing the first 10 procedures on patients with FEV_1 greater than 0.5,

PaO_2 greater than 50 mmHg and a $PaCO_2$ lesser than 50 mmHg (while on supplemental oxygen).

The most common method of catheter insertion is the modified Seldinger technique. Transtracheal Systems has divided the process into four phases, and the readers are urged to familiarize themselves with all phases in detail prior to performing the procedure (www.tto2.com). Phase 1 consists of patient education and selection. It is crucial to have a dedicated nurse trained in TTO catheter care and complications. We have the patient and family meet with our nurse to ensure that the patient has the proper social support network and will be able to care for the catheter. Patients are encouraged to meet with other patients who currently use the TTO delivery method, as well as watch an instructional video. If the patient and nurse agree that TTO is a possibility, the patient then meets with our Interventional Pulmonary team for a medical evaluation including history and physical examination with a focus on baseline indices of oxygenation, history of bleeding diatheses and neck anatomy.

Phase 2 consists of placing a 9-F stent with the purpose of creating a tracheo-cutaneous tract. As there have been studies that suggest a higher incidence of coughing and subcutaneous emphysema when oxygen flow is initiated immediately after catheter insertion [11], this is only a stent and oxygen is not delivered until Phase 3. The patient is typically seated in a chair and oxygen is continued via NC. The chain which will later secure the TTO catheter is placed around the neck, and the point over the trachea that will provide maximum stability for the catheter is marked, as is the thyroid cartilage, cricoid cartilage and notch of the manubrium. After application of chlorhexidine (or topical iodine) to sterilize the skin, the appropriate site is infiltrated with 1.5% lidocaine with epinepherine. The needle is inserted into the trachea, and several cubic centimeters of lidocaine are instilled into the trachea to reduce cough. The needle should be quickly removed to avoid injury to the posterior tracheal membrane during the ensuing coughing. A scalpel with a #15 blade is used to make a 1-cm vertical incision through the skin and subcutaneous fascia, and a syringe attached to an 18-GA thin wall needle is directed through the incision perpendicular to the trachea, and through the intercartilaginous ligament. After intra-tracheal position is confirmed by the free aspiration of air, the syringe is removed and a guidewire is passed into the distal trachea. The needle is withdrawn, and a 10-F dilator is fed over the guidewire to bluntly dilate the tracheal stoma. The dilator is removed over the wire, the stent placed over the guidewire, the guidewire is then removed and the stent sutured in place with 3.0 nylon suture. The procedure kit comes prepackaged (Figure 11.1), and it is crucial to remember to send the patient home with the necklace, the guidewire, the wire-cutting scissors and instruction booklet. A posteroanterior and lateral chest radiograph is then obtained to confirm proper placement. This is an outpatient procedure, and patients are given a prescription for cephalexin (250 mg every 6 h for seven days) and benzonatate (tessalon perles) as needed for cough. Patients are also taught to clean the site twice daily, and instructed to report any signs of infection.

One week later, the patient returns to the office, and the stent is removed over a guidewire and the SCOOP 1 catheter (also 9 F) is inserted (Phase 3). The SCOOP 1 catheter is 20 cm long, with an 11-cm intratracheal segment, and a single distal orifice. For the next 5–7 weeks, patients clean the catheter in place twice a day with saline and a cleaning rod. Patients are given instructions to call immediately should any sign of mucus obstruction develop. These include worsened cough or dyspnea, a whistling sound from the humidifier or a sudden pop when the oxygen tubing is disconnected. Patient visits during Phase 3 should be on an as-needed basis, with much of the care and monitoring being coordinated by the nurse specialist.

After 8 weeks, when the tract is mature, the patient returns to the clinic (Phase 4), and is instructed on how to remove and reinsert the TTO catheter for cleaning. This is initially done twice daily, but can be tailored to the individual depending on the frequency of mucus ball formation. Once in position, the catheter is held in place by a chain, and when covered by a scarf, or collard shirt, is fairly inconspicuous (Figure 11.2).

The other method of TTO placement is the FastTract method. This method, originally described by Lipkin *et al.*, created a tracheal stoma just large enough to accommodate a #4 Jackson tracheostomy tube [20]. The tracheostomy tube

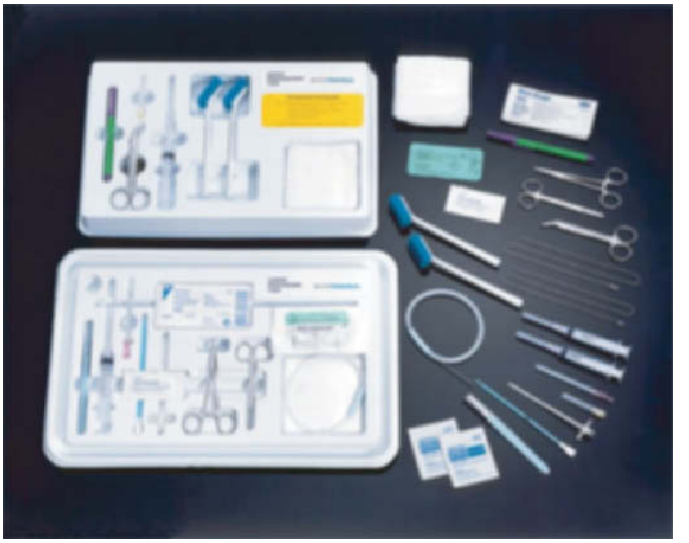

Figure 11.1 Transtracheal oxygen procedure tray. (Reproduced with permission from Transtracheal Systems, Denver, CO.)

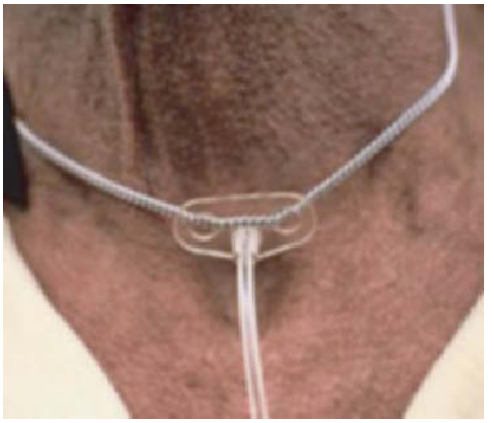

Figure 11.2 Transtracheal oxygen catheter in place. (Reproduced with permission from Transtracheal Systems, Denver, CO.)

was removed over a guide wire on postoperative day 1, and the SCOOP 1 catheter was inserted. They found this technique was associated with up to a 75% reduction in time to tract maturity. Since Lipkin's description in 1996, the procedure has evolved, though it is still carried out in the operating room. A cervical lipectomy is performed through a 1.5–2 cm vertical incision. The skin is then sutured to the inferior aspect of the sternothyroid muscles, creating an epithelized tract. The trachea is entered with a scalpel in the intercartilagenous space, and a punch dilator is used to resect a small window of cartilage. The main advantage of the FastTract method is the initiation of Phase 3, the delivery of oxygen through the catheter, on postoperative day 1.

Clinical studies

In Christopher's study of 100 patients with chronic hypoxemia, the mean baseline room-air PaO_2 was 44 mmHg. Patients experienced a significant reduction in flow rate (mean, 55%), including a 30% reduction in flow rates during exercise. The authors also report significant reductions in polycythmia, despite prior use of oxygen via NC. The most common adverse event was the development of "symptomatic mucus balls" in 10 patients during Phase 3 (while the catheter was being cleaned in place). These mucus balls were described as pea to marble sized accumulations of inspissated mucus that were either "coughed up spontaneously or stripped off the catheter when it was removed over the guide for cleaning" [10]. There were no cases of mucus ball formation in Phase 4, when the patient removes the catheter for daily cleaning. Only 2 of the 100 patients elected to revert back to NC oxygen during the mean follow-up of 35 weeks (up to 2 years) (an additional 2 patients decided not to have the procedure repeated after their initial tract was lost). In addition to the benefits of maintaining oxygenation with reduced flow rates, the authors

suggest improved self-image, and compliance with prescribed 24 h/day oxygen therapy [10].

Hoffman and colleagues compared TT and NC oxygen delivery in a group of 20 patients with moderate COPD, with a follow-up of 1 year [21]. Although TTO resulted in a significant reduction in oxygen flow rates at both rest and exercise, the oxygen use per month (as measured in pounds delivered) was not changed. A possible explanation for this is the increased compliance seen with TT systems as compared to NC. TTO was associated with an improvement in 12-min walk distance, as well as a significant reduction in days hospitalized for respiratory illness. The authors also estimate that TTO use would result in a cost savings of approximately $55 000 per patient over the first year.

The mechanism of improved exercise tolerance does not seem to be related to changes in arterial oxygenation [8,22]. Other potential mechanisms include a decrease in inspired minute ventilation, a reduction in dead space, a mechanical unloading of the respiratory system resulting in a decreased work of breathing or alterations in airway receptor stimulation [23,24]. Some of these effects are observed whether air or oxygen is administered through the transtracheal catheter, and therefore may relate more to the flow of gas in the trachea as opposed to the FiO_2. Additionally, a "training effect" may occur as patients become less self-conscious about wearing oxygen and become more active [9].

The use of pulsed TTO to further conserve oxygen has also been investigated. In comparison with continuous flow TTO, pulsed TTO was found to improve the efficiency of oxygen delivery by a factor of 3 : 1. Given the 2 : 1–3 : 1 improvement of TTO compared with continuous flow NC oxygen, pulsed TTO is thought to have an efficiency of 6 : 1–7 : 1 over standard continuous nasal oxygen [25]. As expected, bulk liquid oxygen use over the course of a month has also been shown to be substantially lower with pulsed TTO as compared with continuous flow TTO and both pulsed and continuous NC oxygen [26].

Transtrocheal oxygen has been shown to be an effective alternative to continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnea (OSA). Farney *et al.* compared CPAP, TTO, transtracheal air and NC oxygen in a group of patients with severe OSA [27]. Though nasal CPAP was the most effective modality for treating both hypoxemia and apnea/hypopnea, TTO also significantly improved both parameters.

Complications

Complications associated with TTO are not uncommon. In Orvidas' study, 30% of patients had at least one early complication (seen in the first 3 months) and 73% had at least one late complication (post 3 months), though the majority (95%) of complications were considered minor and were easily treated [28]. Complications may be associated with the placement of the catheter, mechanical complications from the catheter itself or related to the flow of oxygen directly into the trachea. Procedural complications include cough, pain at the insertion site, bleeding, bronchospasm, catheter misplacement either superiorly or into the mediastinum, pneumomediastinum and pneumothorax. Instillation of oxygen directly into the trachea can result in the formation of mucus balls, which can occasionally become large enough to obstruct the trachea [13,29–35]. Factors that increase mucus ball formation include higher oxygen flow rates ($\geq$5 L/min at rest), patients with poor cough ($FEV_1 < 0.5$) and patients with a history of mucus production (i.e. bronchiectasis). Weekly stripping of the catheter and the use of humidity can reduce mucus ball formation [10,19]. The patient needs to be educated about signs and symptoms consistent with mucus ball formation. Any worsening dyspnea, wheezing, change in cough or dysphonia needs to be taken seriously and early bronchoscopy is recommended. Due to the risk of worsening central airway obstruction, we recommend rigid bronchoscopy as the modality of choice. Catheter dislodgement may also occur, and the stoma may close within several minutes if this occurs during Phase 3.

In a study of 40 patients, Hoffman and colleagues report a 25% incidence of symptomatic mucus ball formation during Phase 3 [2]. They felt the incidence to be higher in patients requiring greater than or equal to 4 L/min, and in patients using the SCOOP 2 catheter. Thus, after the initial 20 patients were enrolled in the study, they continued to use

the SCOOP 1 catheter during Phase 4. Of note, the SCOOP 2 catheter has been discontinued. Over a follow-up of 629 months, 5 patients (12.5%) elected to discontinue TTO. Reasons included dislike of the delivery system ($N = 3$), hemoptysis ($N = 1$) and severe arthritis resulting in difficulty in care of the catheter ($N = 1$).

The catheter tip may cause irritation of the tracheal mucosa resulting in cough, pain or mucus ball formation. This is often seen if the angle of the catheter is too perpendicular to the airway wall, especially when oxygen is flowing through the catheter (Phases 3 and 4). Accurately sizing the catheter by obtaining a PA and lateral chest x-ray is crucial. The catheter tip should be 2–4 cm proximal to the carina. Additionally, Sciurba and colleagues recommend obtaining the radiographic studies at end-expiration, as opposed to end-inspiration, for a more accurate assessment of catheter position [36].

Other complications include cephalad displacement of the catheter, keloid/granulation tissue formation, cellulites, chondritis and decannulation. With a chronic tract, the catheter can usually be reinserted, however, as with early catheter dislodgements, the catheter should be reinserted as soon as possible. This can be particularly troubling for patients who do not live near the center where TTO catheters are placed, as only a minority of pulmonologists are familiar with TTO placement and their complications. One should also note that, as with any procedure, there is a learning curve, both for the physician and the support staff. This may result in a higher incidence of complications in the first several patients, however, with experience, complication rates typically fall [12]. Transtracheal oxygen catheters are generally well tolerated, even in long-term follow-up. Orvidas *et al.* reviewed 56 patients who had TTO catheters in place from 2 days to 6 years (mean 89 days) [28]. Forty-two patients (75%) died with their catheter in place. Of these 42, 12% died within 6 weeks after catheter placement, and 57% died within 1 year. Only seven patients (17%) survived longer than 3 years. Death was unrelated to the TTO catheter in all patients. Of the 14 patients who had the catheter removed before death, 4 were removed for chronic mucus plugging. In the largest series to date, only 3–4% of patients elect to return to NC oxygen [10,12].

Summary

Though TTO has been available for the last 20 years, it remains an underutilized technique. Likely reasons for this are lack of training of pulmonary fellows in the procedure, as well as the up-front investment in staff education and time required to make a TTO program successful. Given the significant improvements in physiologic parameters and patient satisfaction, with a relatively low complication rate, it is likely that TTO use will continue to increase. As with the incorporation of any new procedure into one's practice, I would encourage preceptorship/mentoring with physicians who have significant experience with patient selection, TTO catheter placement and post-procedure management. The guidelines published by the American College of Chest Physicians suggest the performance of 10 supervised procedures, followed by at least 5 per year in order to maintain competency [37].

Percutaneous tracheotomy

Introduction and history

Although tracheotomy has probably been performed for more than 3000 years, the Italian anatomist and surgeon Fabricius is credited with first describing a tracheal cannula in 1617. Another Italian surgeon Sanctorio Sanctorius provided the first description of percutaneous tracheotomy in 1626. He used a "ripping needle" to introduce a silver cannula into the tracheal lumen, and then removed the needle. In 1869, Trendelenberg developed the first cuffed tracheostomy tube. It wasn't until early twentieth century, however, that tracheotomy became a popular procedure due to the standardization of open surgical tracheotomy (ST) by the famous American surgeon Chevalier Jackson. In the 1930s, tracheotomy was advocated as an effective way to provide bronchopulmonary toilet in patients with polio. With the increasingly widespread use of positive pressure ventilation in the 1950s considerable energy was focused on the development of tracheostomy tubes as a means of providing long-term ventilatory support. In the late 1960s, Toye and Weinstein used a Seldinger guide wire to safely introduce a cannula into the tracheal lumen, and in 1985, Ciaglia described what has

now become one of the most popular techniques for percutaneous dilational tracheostomy (PDT) [38–41].

Indication and timing

Since the development of high-volume, low-pressure cuffs for endotracheal tubes in the 1960s, there has been a significant reduction in tracheal injury as a result of endotracheal intubation. However, prolonged translaryngeal intubation continues to be associated with several complications including laryngeal injury, glottic and sub-glottic stenosis, tracheomalacia and stenosis as well as an increase in ventilator associated pneumonia and mortality [42–44]. The acute and long-term complications of artificial airways have recently been reviewed in detail [44,45]. Tracheotomy is associated with its own procedural complications as well as complications arising from the tracheostomy tube itself (see later). Some authors therefore recommend early tracheotomy in order to avoid the *additive* complications of the translaryngeal tube and the tracheostomy tube. In 1989, the American College of Chest Physicians published their Consensus Conference on Artificial Airways in Patients Receiving Mechanical Ventilation [46] and recommended tracheotomy when the anticipated need for an artificial airway was more than 21 days. Additionally, the procedure should be done "as early as possible," and "once the decision is made, the procedure should be done without undue delay" [46].

In a review of the literature encompassing 396 patients, Maziak and colleagues sought to answer whether the timing of tracheotomy influences the duration of mechanical ventilation, tracheal injury or the clinical status of patients in the ICU [47]. Unfortunately, they concluded that the currently available trials have not provided clear guidelines, and suggest that the decision needs to be individualized for each patient. In a post hoc analysis of a prospective cohort study, Kollef's group found that patients who receive a tracheotomy have a lower mortality than those who do not, despite an increase in total days on mechanical ventilation and hospital length of stay [48]. Other studies support the use of early tracheotomy to reduce ICU and total ventilator days [49,50].

A recent randomized trial comparing early (within 48 h of intubation) versus delayed tracheotomy (performed at days 14–16) found a significant reduction in mortality (32 versus 62%), pneumonia (5 versus 25%) and unplanned extubations in patients receiving early tracheotomy [51]. Additionally, ICU length of stay and days requiring mechanical ventilation were both significantly reduced in the early tracheotomy group. The main criticism of this study lies in the general inability of intensivists to predict which patients are going to require prolonged mechanical ventilation.

Heffner's recommendation that "the timing of tracheotomy for an individual patient, however, is a complex decision . . .," and "such complex decisions are best made by individualizing care" should be the current standard of care [52].

Contraindications

The major contraindication of any procedure is its performance by an inexperienced provider. Guidelines for the performance of percutaneous tracheotomy were recently published [37], and as with TTO, I recommend precepting a physician experienced with the procedure as much as possible. As most percutaneous tracheotomies are elective in nature, patients should be hemodynamically stable and coagulopathy should be corrected as much as possible. Other contraindications include overlying cellulitis or the presence of a visible/palpable vessel in the desired location. Anatomic variations such as the inability to hyperextend the neck due to cervical spine disease, overlying goiter, a short neck or severe kyphosis can make the procedure more difficult. There are case reports, however, of safely performing PDT in almost every patient category, including the morbidly obese [53], those who have had prior tracheostomy [54] and in patients with severe thrombocytopenia [55]. As the translaryngeal tube may be inadvertently removed during the procedure, patients who require a high FiO_2 or PEEP in order to maintain oxygenation are at higher risk for perioperative hypoxemia.

PDT Kits

The two most popular kits for PDT are the Per-Fit PDT kit (Portex Inc., Keene,

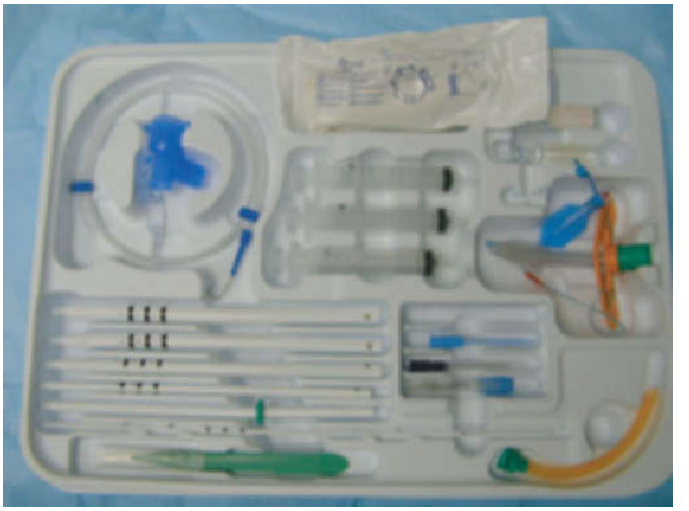

Figure 11.3 Per-Fit percutanteous tracheotomy procedure tray. (Reproduced with permission from Portex Inc., Keene, NH.)

Figure 11.4 Blue Rhino percutaneous tracheotomy procedure tray. (Reproduced with permission from Cook Critical Care, Bloomington, IN.)

NH; Figure 11.3; http://www.portex.com/airway/products/select5.asp?autonum=23http://www.) and the Ciaglia Blue Rhino percutaneous tracheostomy introducer tray (Cook Critical Care, Bloomington, IN; Figure 11.4; http://www.cookcriticalcare.com/features/blue_rhino.html). The Per-Fit kit comes with four straight dilators of increasing size and a tapered Portex tracheostomy tube with an inner diameter of 7, 8 or 9 mm. The kit has a preparation tray and a separate procedure tray. The Cook kit contains three tracheostomy tube-loading dilators and the tapered Blue Rhino tracheostomy dilator. The desired tracheostomy tube must be obtained separately, or can be ordered with the introducer kit. The technique is essentially the same for these two kits, with the exception of performing serial dilations with the Per-Fit kit as compared to one gradual dilation with the Blue Rhino kit. We typically place an 8-mm tracheostomy tube, which allows for adequate pulmonary toilet and ventilation, but the choice of the tube is individualized to the patient. Obese patients may require a tracheostomy tube with extra horizontal length. Another technique, developed by Griggs

and colleagues [56] uses a curved dilating forceps over a wire; however, this technique has become less popular with the advent of the previously described kits, and one study suggests a higher incidence of operative complications [57].

The PDT procedure

Percutaneous dilational tracheostomy is generally performed at the bedside in the ICU. Pre-procedure evaluation includes a careful review of the history and respiratory status of the patient, as well as a careful physical examination that is focused on the neck and tracheal structures. Especially when starting to do PDT, patients should have ideal anatomy such as a relatively long, thin neck, the ability to hyper-extend the neck and no underlying vessels. Pertinent lab studies include a platelet count, PT, PTT as well as BUN to evaluate for uremia. PDT can be safely performed in patients with uremia; however, we pretreat these patients with DDAVP, and consider a PT/PTT less than 1.5 times control and a platelet count greater than 50 000/mm^3 acceptable [58]. Patients must also have adequate intravenous access. We generally refer high-risk patients for surgical tracheotomy.

Optimal staffing includes an anesthesiologist or other physician who is trained in airway management stationed at the head of the bed to control the translaryngeal endotracheal tube and administer medication. We favor the use of sedation, analgesia and short-acting paralysis in order to minimize patient discomfort and coughing, and typically use propofol, fentanyl and vecuronium. A nurse familiar with the procedure should be available to monitor vital signs and the cardiorespiratory status of the patient. At our institution, we perform bronchoscopy with therapeutic aspiration of any retained secretions prior to the procedure.

A rolled towel is placed between the patient's scapula in order to hyperextend the neck and maximally increase the distance between the tracheal rings. The skin is prepped with chlorhexidine, and a sterile field is created with a fenestrated drape. The FiO_2 is increased to 0.9–1.0 and the ventilator is set with a backup rate as the patient will be sedated and/or paralyzed.

Anatomic landmarks include the thyroid cartilage, the cricothyroid membrane, the cricoid cartilage and the tracheal rings (Figure 11.5). It is also important to palpate for overlying vessels and the thyroid. The ideal entry site is between the first and second, or second and third tracheal rings. Some data suggest a higher incidence of tracheal stenosis if the cricothyroid membrane is involved, and if the tracheostomy tube is placed too inferiorly, the risk of a tracheo-innominate artery fistula increases. The skin is infiltrated with up to 5 cc of 1.5% lidocaine with epinephrine. After an initial 1.5 cm horizontal incision through the skin and subcutaneous fascia, the soft tissue is bluntly dissected and the tracheal rings are palpated. One option at this time would be to withdraw the translaryngeal tube to just inferior to the vocal cords; however, PDT can safely be performed next to the tube as well. If the translaryngeal tube is pulled back, this can be done with bronchoscopic visualization; however, we try to limit the bronchoscopy time in order to reduce the likelihood of hypercapnia [59] – especially in patients with elevated intracranial pressure. It is crucial to avoid damaging the bronchoscope with the introducer needle. The cuff on the translaryngeal tube is deflated to avoid puncturing it with the needle. One should note that the trachea dives posteriorly as it progresses inferiorly through the chest. The insertion angle of the introducer should be perpendicular to the trachea (not the bed/floor). The trachea is then entered with a syringe containing 5 cc of lidocaine or saline attached to the introducer needle. Aspiration of air confirms the proper location of the needle in the lumen of the trachea. Holding the needle in place, the syringe is removed and a J-tipped guide wire is advanced in the direction of the carina. The tract is initially dilated with the short 10-F (Per-Fit kit) or 14-F (Blue Rhino kit) dilating catheter. For the Per-Fit kit, an 8-F guiding catheter is placed over the guide wire, and the tract is sequentially dilated with four progressively larger dilators. The Blue Rhino kit uses a single tapered dilator. The tracheostomy tube is then inserted on a separate obturator/dilator, and the cuff is inflated. Adequate position is confirmed via bronchoscopy through the tracheostomy tube in addition to observing return of tidal volume from the ventilator once the ventilator circuit is connected to the tracheostomy tube. The tracheostomy tube is secured with a strap such that one finger can be placed between the strap and the skin,

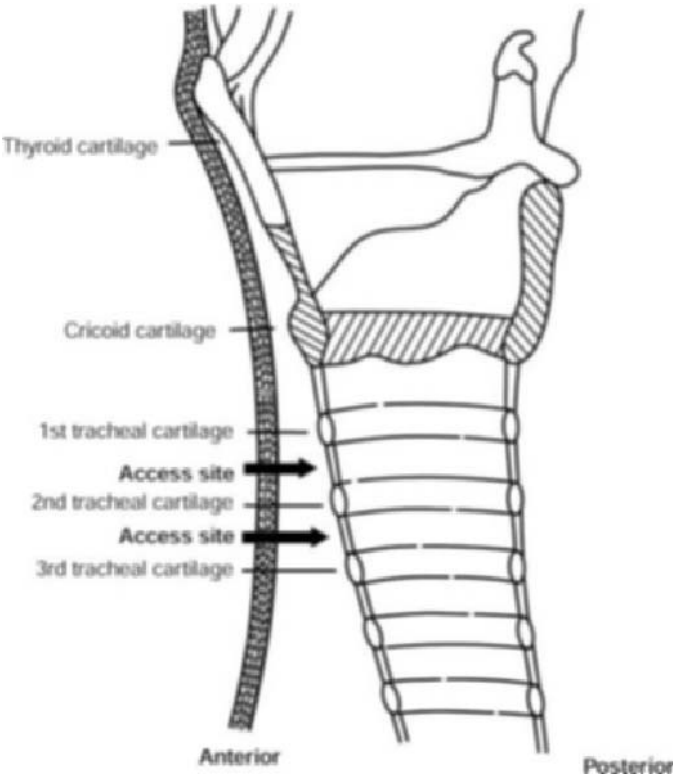

Figure 11.5 Sagital view of relevant tracheal anatomy. (Reproduced with permission from Cook Critical Care, Bloomington, IN.)

and generally does not need to be sutured in place [58]. It is crucial that one operator always hold the tracheostomy tube as it is being secured. If accidental decannulation occurs, the patient should be reintubated with a translaryngeal endotracheal tube with the cuff of the tube distal to the stoma. Attempts at tracheostomy tube reinsertion should only be done when the airway is secure, and as the tract is immature, the introducer needle and guide wire should be used to avoid misplacement into the mediastinum.

Once in place, the tube will require care primarily provided by nurses and respiratory therapists. Wright and VanDahm have recently reviewed the long-term care of the tracheostomy patient [60]. The stoma should be cleaned on a twice daily basis with a mixture of 1 : 1 hydrogen peroxide and sterile saline. The tracheostomy tie, preferably the foam-padded Velcro fastener, should be checked routinely such that only one finger can be placed between the fastener and the skin on each side of the neck. If the fastener is too loose, the tracheostomy tube can become dislodged, or cause erosion to the posterior tracheal membrane. As reviewed in the section "Complications of ST versus PDT" later, post-procedure bleeding is generally rare. Early bleeding is often due to superficial vessels and can be controlled by injecting 1.5% lidocaine with epinephrine (1 : 200 000), 2 cc in the 12 : 00, 3 : 00, 6 : 00 and 9 : 00 positions. Rarely, surgicel or gellfoam may be required. Bleeding after 48 h should prompt one to suspect the possibility of a tracheo-innominate artery fistula. This is an emergency, and prompt surgical consultation should be obtained. As with endotracheal tubes, tracheostomy tube cuff pressures should be monitored, and kept below 25 mmHg in order to avoid focal ischemic necrosis [61]. Once ventilation is no longer required, thought should be given toward changing the tube to an uncuffed tube and/or proceeding with downsizing and decannulation.

A Comparison between surgical and percutaneous tracheotomy

There have been several recent well-designed prospective trials, as well as randomized controlled trials and meta-analyses comparing PDT and ST. Some of the more recent randomized trials and meta-analyses will be reviewed.

Holdgaard *et al.* randomized 60 patients to receive PDT via the serial dilator technique versus ST, both performed in the OR. PDT was performed significantly more quickly, and was associated with a reduction in both bleeding and infection [62]. Freeman and colleagues confirmed the reduced procedural time of PDT compared with ST (20.1 versus 41.7 min), and also found that PDT charges were significantly less ($1569 versus $3172), though the majority of this saving was due to the lack of OR charges associated with PDT [63]. Other studies have found that once the decision is made to perform tracheotomy, OR scheduling can significantly delay the procedure [64]. Despite this delay, the duration of translaryngeal intubation, hospital or ICU length of stay does not differ between the procedures [63,65].

Another benefit of PDT is the ability to perform the procedure at the bedside, minimizing any transport associated risks. Massick and colleagues randomized 100 patients to PDT or ST performed at the bedside in the ICU and compared the results to an additional 64 patients who had ST performed in the OR [66]. There was no significant difference in duration of the procedure between all of the groups. Patients receiving ST in the OR had a significantly higher incidence of perioperative complications than those who received the procedure at the bedside, though these patients did not meet the authors' criteria for performance of the procedure at the bedside, and therefore tended to be more prone to complications. The incidence of postoperative complications did not differ between the bedside and OR groups. In the patients selected for bedside procedures, there were no differences in perioperative complications, though PDT had a higher incidence of postoperative complications when compared to bedside ST. This was due to a higher incidence of tube displacement with an inability to replace the tube in the PDT group. It is unclear, however, why more of the percutaneously placed tubes were displaced, as both PDT and ST tubes were sutured in place and secured with a standard tie. Additionally, as stated earlier, if decannulation occurs within the first seven postoperative days, the patient should be reintubated and only then should one attempt to reinsert the tracheostomy tube. Performing the procedure at the bedside resulted in a significant reduction in cost, as compared to performing the procedure in the OR, and ST performed at the bedside, was significantly less expensive than PDT ($436 versus $910). This resulted from the additional charges associated with using bronchoscopic guidance for PDT as well as the charges for the PDT kit [66].

Complications of ST versus PDT

In general, the complications of bedside percutaneous tracheotomy in the ICU are quite small, and compare favorably to ST performed either in the operating room or at the bedside [62–64,67]. The more frequent complications include bleeding, infection, accidental decannulation, paratracheal insertion, injury to the posterior tracheal membrane, pneumothorax, tracheal ring fracture and the development of tracheal stenosis. Though some studies suggest a higher incidence of bleeding and infection with ST as compared to PDT [62,64,68–71], others report no significant difference [66,72–74]. In a review of 1116 cases, Moe *et al.* found an overall procedure related mortality rate of only 0.4% [67]. Major hemorrhage and pneumothorax occurred in 0.6%, wound infection in 0.8%, paratracheal insertion in 0–6%, accidental decannulation in 0–2% and minor hemorrhage in up to 3% [67].

A meta-analysis investigating complications of ST and PDT was recently published by Dulguerov and colleagues [75]. As most of the PDT series have been published since 1985, studies examining ST were separated by publication date (1960–1984 versus 1985–1996) in order to provide a timely comparison with the PDT studies. Serious perioperative complications, including death, cardiorespiratory arrest, pneumothorax and pneumomediastinum were significantly less common in the ST (1985–1996) group as compared with the PDT and the ST (1960–1984) groups (86 versus 149 versus 239 per 10 000 cases, respectively). Intermediate perioperative complications such as

desaturation, hypotension, lesions of the posterior tracheal wall were also less common in the ST (1985–1996) group. It is important to note, however, that the incidence of these complications is quite small, with injury to the posterior tracheal wall occurring in 6 out of 10 000 patients in the ST (1985–1996) group and in 50 out of 10 000 in the PDT group. Although the rates of serious postoperative complications (death, tracheoesophageal fistula, mediastinitis, sepsis, postoperative cannula obstruction or displacement and tracheal stenosis) were similar in the ST (1985–1996) and PDT groups, intermediate postoperative complications including pneumonia and tracheomalacia were seen less commonly in the PDT group. Minor hemorrhage and wound infections were also less common in the PDT group. The authors also suggest that bronchoscopic visualization during PDT reduces the incidence of intermediate and minor perioperative complications [75].

Freeman and colleagues performed a meta-analysis of five prospective studies involving 115 patients receiving PDT (via the Ciaglia technique) and 121 STs [76]. Though they found no significant difference in the overall operative complication rate, PDT was associated with a reduction in operative bleeding. Again, postoperative complications were significantly less common in the PDT group. The authors suggest that the difference in results concerning perioperative complications differ from the meta-analysis of Dulguerov *et al.* because the latter study included observational studies in addition to prospective studies, as well as studies in which PDT was performed by several techniques.

Although the use of bronchoscopic visualization has been proposed as a method to reduce the complication rate, there are no definitive data to support this, and some authors do not use bronchoscopy once the learning curve is surpassed [77]. Benefits of performing PDT with bronchoscopic visualization include safe withdrawal of the endotracheal tube, ensuring midline placement of the needle and guide wire, and potentially adverting paratracheal placement or injury to the posterior tracheal wall. Potential complications associated with the use of bronchoscopic visualization include hypercapnia due to obstruction of the endotracheal tube, and damage to the bronchoscope from the introducer needle. Bronchoscopy also prolongs the procedure, and may delay the initiation of the procedure due to unavailability of the bronchoscopy cart and respiratory therapist, resulting in prolonged ICU and hospital length of stay. Additionally, the use of a bronchoscope may require an additional physician and increases the costs associated with the procedure. Furthermore, some authors suggest that the use of the bronchoscope only serves to visualize the damage and does not reduce the incidence of complications.

Again, if the tracheostomy tube is inadvertently removed before a mature tract has developed (typically in ~7 days), orotracheal intubation should be performed and the cuff of the tube placed distal to the tracheal stoma. Reinsertion of the tracheostomy tube through an immature tract typically results in the generation of a false channel in the subcutaneous tissue anterior to the trachea. After a secure airway has been established, the stoma can then be re-dilated under more controlled circumstances [58]. Additionally, because of this risk, we routinely use an exchange catheter when replacing tracheostomy tube within the first 2 weeks.

Tracheal stenosis can occur after both translaryngeal intubation and tracheotomy. The stenosis can occur in the subglottic space, at the level of the tracheal stoma, or at the level of the cuff of the endotracheal/tracheostomy tube. As almost all patients with tracheostomy tubes have had orotracheal tubes, it can be difficult to identify the causal factor, unless the stenosis is at the level of the stoma. With this in mind, the overall incidence of clinically significant tracheal stenosis is estimated at 1.8% [78]. This represents a marked decrease since the 1960s, and is due in part to the development of high-volume, low-pressure cuffs [79]. It is also important to understand that tracheal stenosis is generally not clinically significant until there is a 75% reduction in luminal diameter, and that stridor will not develop until the luminal diameter is less than 5 mm [79]. In a study of 83 patients receiving PDT and ST, Stoeckli *et al.* collected laryngotracheal specimens from 21 patients who had died within the average 336 days of follow-up [68]. Although PDT was associated with a higher incidence of cartilage fractures at the introduction site, none of the patients in either group developed clinically significant tracheal stenosis.

Credentialing

As PDT is a relatively simple procedure, it is being performed more and more by intensivists who have not had formal surgical training. Regardless of specialty, the operator should be proficient in airway management including emergent airway techniques. Formal training in PDT is essential, and should begin with hands-on instruction, practicing either on tracheal models, animal tracheas or cadavers. It is crucial to have guidance from an expert, especially when performing the first several cases. The guidelines published by the American College of Chest Physicians suggest the performance of 20 supervised procedures, followed by at least 10 per year in order to maintain competency [37].

Summary

Percutaneous dilationel trachcostomy is currently one of the most commonly performed procedures in the ICU. It has been shown to be both safe and cost-effective when compared to surgical tracheostomy, and is quickly becoming the tracheotomy procedure of choice in patients requiring prolonged mechanical ventilation. As with any procedure, it should be performed by experienced personnel with additional expertise in airway management. Although the cost savings are probably negligible compared to ST performed at the bedside, PDT may be associated with less delay once the decision to perform tracheotomy is made. Larger randomized trials are needed to define the exact role of PDT as well as the best time to perform tracheotomy in general. In the meantime, the current literature supports PDT as a favorable alternative to ST.

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12 CHAPTER 12

Bronchoscopic lung volume reduction

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Lung volume reduction surgery

Lung volume reduction surgery (LVRS) has been shown in the recently completed National Emphysema Treatment Trial (NETT) and in numerous smaller controlled trials, to improve lung function, exercise capacity and quality of life in selected patients with advanced emphysema [1]. In a subset of these patients, LVRS also reduces mortality as compared to medical treatment alone. However, even when performed at experienced centers, LVRS is associated with significant morbidity, mortality (5.2% at 90 days) and cost. Furthermore, when expressed in terms of quality adjusted life years, LVRS is more expensive than many currently accepted surgical interventions for end stage diseases that are refractory to medical therapies, including coronary artery bypass grafting, cardiac transplantation and lung transplantation [2] (see Table 12.1).

Lung volume reduction surgery alters respiratory system physiology in several ways, and improvements following treatment result from a combination of physiological effects [3–7]. As originally proposed by Brantigan in the 1950s [8], and convincingly demonstrated by Fessler *et al.*, LVRS partially normalizes the mechanical relationship between the emphysema lung and surrounding chest wall, increasing vital capacity and isovolume transpulmonary recoil pressures. This appears to be the primary mechanism responsible for physiological improvement following LVRS. Other factors also appear to contribute to the physiological and symptomatic improvements that follow LVRS treatment in many patients, however. Increases in recoil pressures increase airway conductance in a subset of patients, presumably by raising isovolume airway transmural pressures, expanding airway through tethering [9]. The reduction in lung size that follows LVRS normalizes diaphragmatic and chest wall dimensions, improving ventilatory capacity by shortening the operating length over which the respiratory muscles function. In a smaller number of patients, temporary improvements in oxygenation have been observed as a result of local changes in lung impedance that act to normalize ventilation–perfusion matching. LVRS may also improve dynamic lung mechanics by eliminating lung zones with the longest expiratory time constants, reducing the tendency for gas trapping and dynamic hyperinflation during exercise [10].

Alternatives to LVRS are being developed that are designed to provide less invasive, safer and less costly ways of achieving the same primary physiological objective: resizing of the lung and chest wall through a reduction in residual volume relative to total lung capacity [9,11–13]. Several different approaches are currently being investigated to

Table 12.1 Cost-effectiveness of LVRS.

Procedure	*Cost per quality adjusted life year (in $)*
CABG	8 000–65 000
Heart transplant	65 000
Lung transplant	130 000–200 000
Lung volume reduction surgery	190 000–300 000

Table 12.2 Bronchoscopic volume reduction therapies being tested.

Product type and methodology	*Affiliated company(s)*	*Available data*	*Relevant publications*	*Stage of development*
Device Endobronchial one-way valves designed to cause mechanical collapse of target areas	Emphasys Medical Inc.	Pilot studies in humans confirming safety and showing limited benefit in selected cases	Lancet 2003;361:124, 931–933 Chest 2003; 124:1073–1080 Am J Respir Crit Care Med 2003;167:A532, A576, A293	Pivotal study ongoing
	Spiration Inc.	Nonclinical studies in normal animals	Chest 2002; 121:201–209 Chest 2003;124:124S	Pilot study ongoing
Application of radiofrequency ablation ballon catheter to burn channels through the lung, reducing closing capacity and residual volume	Broncus Technologies, Inc.	*Ex vivo* studies in human emphysema lungs; intra-operative feasibility study	Ann Thorac Surg 2003; 75(2):393–397 J Thorac Cardiovasc Surg 2003; 125:1294–1299	Pilot study ongoing
Biological agent Administration of bioactive reagents to cause shrinkage of damaged areas of lung using tissue engineering principles	Aeris Therapeutics, Inc.	Nonclinical studies in large animal models of emphysema	Am J Respir Crit Care Med 2001; 164:295–301 Am J Respir Crit Care Med 2003; 167:771–778 J Bronchol 2004; 11:83–86	Phase 1 trial ongoing

achieve this objective, and clinical trials are beginning in the United States and elsewhere. Initial results suggest that the physiological basis for symptomatic improvement following "nonsurgical lung volume reduction" may not be the same for each of these new methods, and may in fact be distinct from that of LVRS itself. The technology, methodology, published experiences and limitations of each approach are summarized here, and a comparison of the different approaches presented (see Table 12.2).

Lung volume reduction using proximally obstructing devices

Based on the work of Fessler *et al.* [11] and Ingenito *et al.* [6] it appears that lung volume reduction therapy improves respiratory function in emphysema primarily by reducing the size of the hyperinflated lung within the rigid chest cavity. This, in effect, relieves the "restrictive" effects of hyper-expansion, and improves vital capacity. Reduction in lung size, which is essential to effective lung volume reduction, does not necessarily require surgical resection of tissue, and can be achieved by any process that eliminates areas of hyper-inflated lung. Thus lung volume reduction could theoretically be accomplished by placing a device in a proximal airway to obstruct ventilation to the lung distal to the obstruction. Gas "trapped" beyond the obstruction would eventually be absorbed, resulting in sustained collapse of the lung as long as the obstruction remained in place.

Sabanathan *et al.* first tested this concept using bronchoscopically placed silicone balloons designed for vessel occlusion and, later, hospital-manufactured stainless steel stents containing biocompatible sponge. Devices were placed under general anesthesia using a rigid bronchoscope into one or more segments of the bilateral upper lobes of eight patients with end stage emphysema. Five patients experienced subjective improvements. Four had improved MRC dyspnea scores and measured walking distances. One had a reduction in lung volume measured by helium dilution. Periprocedure complications included an expectorated balloon in one patient and bilateral tension pneumothoraces with cardiac arrest in another [14].

Watanabe *et al.* reported the use of a silicone plug designed to obstruct airways, reduce airflow and potentially cause collapse of targeted areas [15]. The endoscopic Watanabe spigot (EWS) is constructed of biocompatible materials, and is deployed through a rigid bronchoscope in a fashion similar to a Dumon stent [16]. Toma *et al.* retrospectively reported the use of EWSs in 23 patients with emphysema for treatment of persistent pneumothorax. Two patients developed upper lobe collapse. Complications included pneumonia in two patients and dyspnea in one [17]. Watanabe also reported another case in which a pneumothorax occurred following treatment of a giant bulla in an emphysema patient using EWSs [15].

Lung volume reduction using one-way valve devices

The failure of proximally obstructing devices to produce effective lung volume reduction in most patients and the occurrence of post-treatment pneumothoraces reveals an apparent flaw in the theoretical basis for such devices; they do not appear to eliminate ventilation to the lung distal to the occlusion. This could result from incomplete blockage of the proximal airway or, more likely, from flow through the extensive collateral ventilation pathways that exist within and between lobes in emphysematous lung [18]. Such ventilation could, paradoxically, lead to hyperinflation of the lung distal to the occlusion as a result of persistent inflow through collateral ventilation pathways together with increased outflow resistance through normal airway channels following device placement.

To try to overcome this problem, two companies (Emphasys Medical Inc. and Spiration Inc.) have developed endobronchial one-way valve devices designed for bronchoscopic deployment to produce targeted collapse within the airways. These one-way valve designs are less likely to be associated with the problem of paradoxical hyperinflation and pneumothorax since pressure build-up in the target areas should allow gas to exit through the one-way valve out into the central airways. The Emphasys Endobronchial Valve (Figure 12.1a) consists of a silicone duckbill one-way valve with a self-expanding nitinol stent retainer. The device is inserted into a segmental or subsegmental bronchus via a delivery device over a guidewire placed by flexible bronchoscopy under anesthesia. The device has been placed in over 100 patients worldwide with limited morbidity and mortality [19]. Toma *et al.* reported their experience in eight patients with severe heterogeneous emphysema (baseline FEV_1 18.4–35.7% predicted; D_{LCO} 24.8–51.4% predicted) who were not candidates for or had refused LVRS. Valves were placed in all the subsegments of one upper lobe in each patient. Four patients showed radiographic evidence of volume reduction in the treated lobe. After 4 weeks, the group as a whole had significant improvements in FEV_1 (0.79–1.06 L; $p = 0.025$) and D_{LCO} (3.05–3.92 mL/min/mmHg). The largest changes were seen in patients with radiographic evidence of volume reduction. There were no significant changes in residual volume (RV), total lung capacity (TLC), shuttle walk distance, or St. George's Respiratory Questionnaire score. Two patients developed pneumothoraces, three had Cardiac obstructive pulmonery disease (COPD) exacerbations, and one had a transient increase in cough [20]. Objective improvements in lung function appeared to decrease with time. Initial increases in FEV_1 and D_{LCO} recorded at 1 week, declined by 25–50% at 30 days [21]. Improvements in symptom and health quality of life scores persisted in several patients, despite declining spirometry, suggesting that spirometry alone may not be the best indicator of response to treatment.

Snell *et al.* reported their experience with the Emphasys valve in 10 patients with severe heterogenous upper-lobe emphysema (FEV_1 18–50%

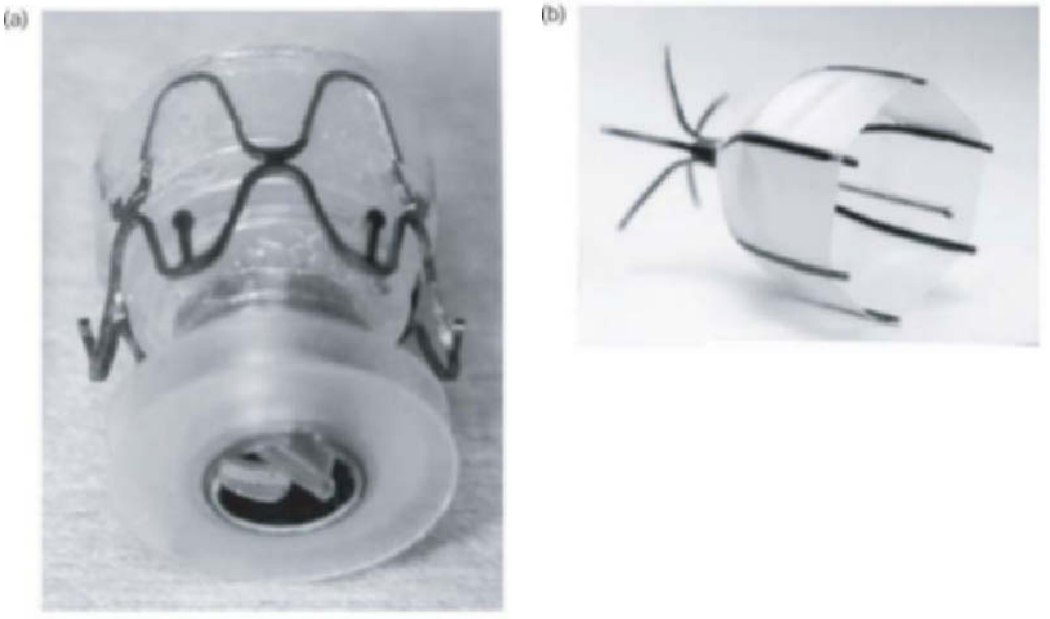

Figure 12.1 (a) Emphasys Endobronchial Valve consisting of a silicone duckbill, one-way valve attached to a nitinol self-expanding stent retainer with silicone seals to occlude the bronchus around the valve. (b) Spiration Intra-Bronchial Valve consisting of an umbrella-shaped polyurethane membrane on a nitinol frame.

predicted; D_{LCO} 21–28% predicted) who were considered candidates for LVRS. Four to eleven valves were placed in subsegments of the upper lobes bilaterally. After 30 days, significant changes were seen in D_{LCO} (7.47–8.26 mL/min/mmHg; $p = 0.04$) and upper lobe perfusion by 99Tc scan (32–27%; $p = 0.02$). No significant changes were seen in FEV_1, RV, TLC, 6-min walk distance, MRC dyspnea score or blood gases. Of note, very little volume reduction was detectable radiographically in any patient. One patient had a pneumothorax, one developed pneumonia and two had COPD exacerbations [22].

Similar results have been reported by Germonpre' *et al.* [23], Venuta *et al.* [24] and Zuhlke *et al.* [25] in abstract form. For the most part, procedures involving the Emphasys valve have been well tolerated. Although only a small fraction of patients have demonstrated spirometric improvements and evidence of lung volume reduction, a higher percentage of patients have demonstrated improvements in exercise capacity, health related quality of life and symptoms. Emphasys is now sponsoring a larger, multicentered, randomized, controlled trial to examine the efficacy of their device, characterize mechanisms of improvement and better define patient selection criteria.

Spiration's device (Figure 12.1b) is intended to work in a similar fashion to the Emphasys valve, but is designed differently. The Spiration Intra-Bronchial Valve is an umbrella-shaped device consisting of a polyurethane membrane on a nitinol frame. It is deployed via a delivery catheter that can be inserted directly through the instrument channel of a bronchoscope. When deployed, the umbrella opens, securing itself against the wall of the airways. The design of the umbrella is such that it produces unidirectional gas flow, and therefore it should function similarly to the Emphasys device. In an animal study of six healthy dogs, placement of 7–8 Spiration valves into the upper lobes resulted in a 13% mean reduction in TLC reduction after 3 months [26]. Subsequent studies in swine confirmed volume reduction, and demonstrated that valves could be easily and safely removed [27]. Human trials of the Spiration device are currently underway.

Both valve systems have the advantage of being removable should complications arise either from their placement or as a consequence of their effects within the airways over time. The devices can also be replaced in the event of mechanical failure, or repositioned to adjust to changes in physiological responses post-treatment, or to changes due to progression of disease.

The major limitation of these valve devices is their apparent lack of physiological effectiveness in producing reductions in lung volume in the majority patients with advanced emphysema, a problem that is most likely due to two distinct factors:

1 the extensive collateral ventilation that exists in the emphysema lung allowing for substantial gas flow around the valves, preventing effective collapse;

2 the high closing volume, and abnormal area–transmural pressure ($A–P_{tm}$) relationship of peripheral airways in the emphysema lung that can result in obstruction of conducting pathways peripheral to an endobronchial valve, rendering the valve completely ineffective in achieving unidirectional emptying.

Studies reported in the literature to date attest to the limited ability of these systems to reduce lung volume in most patients with advanced emphysema, probably a result of the combined effects of these mechanisms. However, it should be noted that some patients seem to have substantial improvements following treatment, and reduction in symptoms using these valves does not appear to require demonstrable reductions in lung volume.

Lung volume reduction using tissue engineering principles

In contrast to the device-oriented approaches described earlier, Aeris Therapeutics' (formerly Bistech) Bronchoscopic Lung Volume Reduction (BLVR) System uses a series of biologically active reagents designed to promote scar formation in diseased areas of lung. The reagents are delivered through a flexible bronchoscope much in the manner of a bronchoalveolar lavage. Three 10 mL injections are administered at each treatment site within the lung to alter the local milieu, and produce a localized scarring reaction that contracts and shrinks the damaged area. The first 10 mL injection is a buffered, trypsin-based solution that inactivates surfactant by cleaving surfactant proteins, and loosens epithelial cells that are essential for maintaining alveolar homeostasis and alveolar patency. The second 10 mL injection, a buffered isotonic salt solution that is followed by application of suction, rinses away inactivated surfactant, detached epithelial cells and residual trypsin. A dual lumen catheter is then passed through the bronchoscope out into the treatment site, and is used to simultaneously deliver fibrinogen and thrombin solutions containing bioactive polymers that polymerize in situ to form a hydrogel. The hydrogel is designed to stimulate fibroblast attachment, proliferation and collagen expression at the site of treatment such that hyperinflated, emphysematous lung tissue is replaced by a contracted organized scar over a period of approximately 8 weeks through the controlled modulation of myofibroblast differentiation and proliferation. This approach has the potential advantage of being less affected by the presence of collateral ventilation, since it does not necessarily rely upon elimination of ventilation to produce volume reduction. However, once administered, the effects of treatment are irreversible.

Ingenito *et al.* reported the use of an earlier formulation of BLVR in a sheep model of homogeneous emphysema. Twelve sheep were randomized to receive BLVR, sham BLVR or surgical LVRS following induction of emphysema with nebulized papain. In the BLVR-treated group, there was a 56% return to baseline TLC and a 65% return to baseline RV, comparable to changes seen in the LVRS group and significantly different from the sham-BLVR group. In two sheep in the BLVR-treated group, sterile abscesses were found at necropsy [28]. A subsequent study by Ingenito *et al.* reported the use of a later formulation of BLVR in six sheep with papain-induced homogeneous emphysema. The authors reported significant reductions in TLC (3.63–3.01 L; $p = 0.02$) and RV (1.43–0.63 L; $p = 0.002$) 3 weeks after BLVR treatment (Figure 12.2). No abscesses were seen [29]. Tsai *et al.* reported the use of BLVR in a heterogeneous model of emphysema in sheep, designed to more closely simulate human heterogeneous disease. Nine sheep were treated with nebulized and bronchoscopically instilled papain,

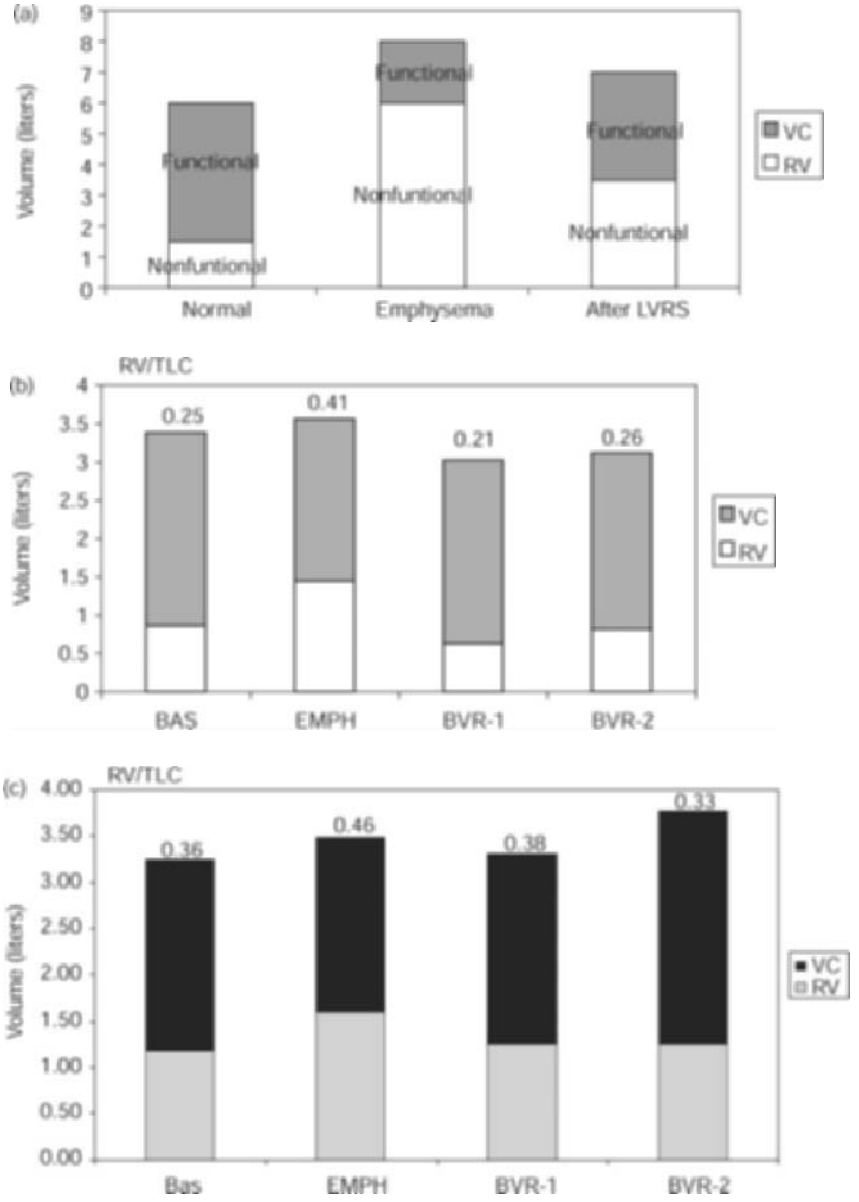

Figure 12.2 Example data showing lung volumes (vital capacity = VC and residual volume = RV) from human patients with emphysema before, and after LVRS (a). Serial measurements from sheep with homogeneous emphysema (b) and heterogeneous emphysema (c) are shown. BVR-1 time point is 1 month after treatment, and BVR-2 time point is 3 months after treatment.

then randomized to receive sham BLVR or BLVR at 6–10 sites. Three months after treatment, in the BLVR group, there was a statistically significant improvement in RV/TLC ratio (0.46–0.33; $p = 0.01$) that was not seen in the sham-BLVR group. In one animal, a large bullous lesion seen on CT scan was visibly reduced following BLVR (Figure 12.3). One animal developed a fever after treatment. There were no other complications and no abscesses were seen at necropsy [30].

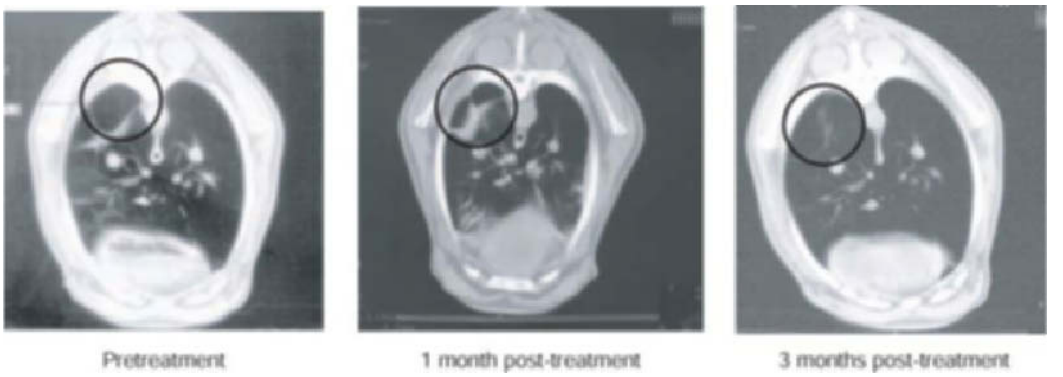

Figure 12.3 Serial images showing resolution of a large dorsal bulla following BLVR treatment in sheep with experimental heterogeneous emphysema.

A human Phase I trial of the Aeris BLVR system is currently underway.

Lung volume reduction using radiofrequency ablation to produce parallel shunt fenestration channels within the lung

Broncus Technologies and Dr. Joel Cooper, the father of modern day LVRS, are developing a completely different minimally invasive therapy for advanced emphysema. Instead of collapsing damaged regions of lung with a device or biological reagent, the Broncus airway bypass procedure creates parallel shunt pathways from damaged lung parenchyma to the central airways using a radiofrequency ablation (RFA) catheter (Figure 12.4). By bypassing the small, floppy, collapsing airways in the damaged area of lung, these shunt pathways lower regional closing volume, resulting in more effective emptying. Rather than altering the static component of residual volume by causing collapse of the treatment area, this approach alters the dynamic component of gas trapping that results from premature airway closure (the volume of which is equal to $P_{tm'} \times C_L$) [5,11]. Although measurements in patients with emphysema suggest that this component of residual volume averaged over the entire lung is not large (because $P_{tm'}$, the transmural pressure at airways collapse at which expiratory flows go to 0 is usually <2 cm H_2O), in a specific area of marked damage, the local $P_{tm'}$ can be quite substantial, and thus altering local closing volume in these areas could, in theory, have a large effect on expiratory flows [9].

The clinical application of this approach is somewhat more complicated than the previously described approaches. First, endobronchial ultrasound is used to locate pulmonary vascular structures within the treatment area in order to avoid damaging them during the procedure. Next, the RFA catheter is used to burn a passage through a nonvascularized region of the bronchial wall into the target damaged region of lung. Finally, a stent is placed in the resulting fenestration to help maintain its patency.

Lausberg *et al.* reported the use of the Bronchus procedure in isolated human emphysema lungs finding 83–155% improvements in FEV_1 using an apparatus designed to simulate forced expiratory maneuvers [31]. Rendina *et al.* reported the feasibility and safety of the procedure in 10 patients undergoing lobectomy for neoplasm and five patients undergoing lung transplant. After the chest was opened and full control of the pulmonary vessels and bronchus was obtained, 1–5 airway bypasses per patient were created through a flexible bronchoscope. There were two instances of minor bleeding ($\leq$20 mL) treated with suction and topical epinephrine [32]. To date, there are no published data of longer term outcomes or functional changes following the procedure.

While innovative and physiologically sound, this approach has several limitations. First, the complexity of the procedure may limit its use to

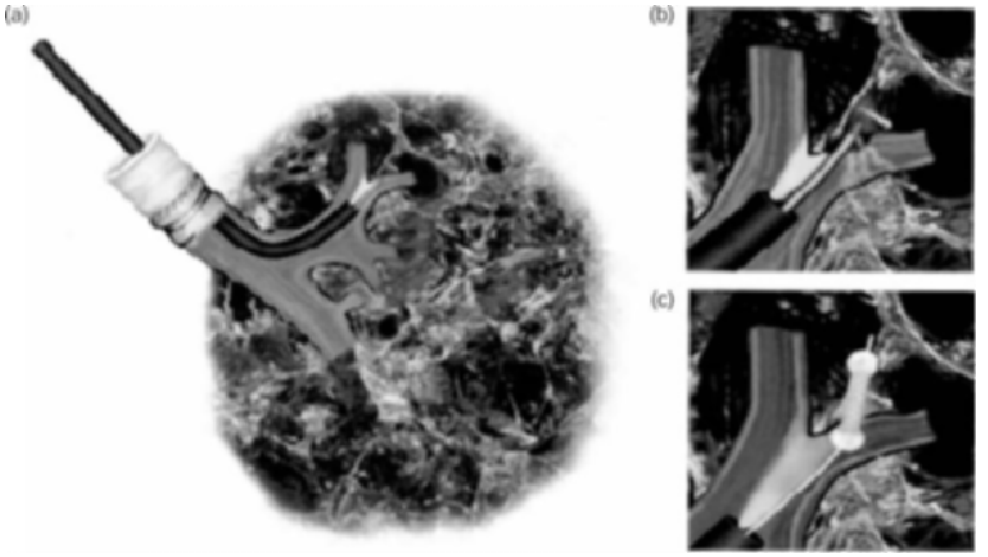

Figure 12.4 Technique for insertion of broncho-pulmonary stents. (a) The flexible bronchoscope is inserted to the level of the segmental bronchus. (b) A radiofrequency probe inserted through the bronchoscope is used to create a hole through the bronchial wall into the adjacent lung parenchyma. (c) A balloon-expandable stent is passed down the bronchoscope and expanded with the proximal end just inside the bronchial lumen.

experienced interventionalists and thoracic surgeons. At the very least, specialized training and equipment will be required to safely perform this procedure which may limit its use to specialized centers. A second challenge is development of a method for maintaining patency of these RFA shunt pathways. RFA damage to the lung is associated with significant scarring, and tissue contraction. The tendency for these pathways to close, and ability to successfully modulate closure, will be a critical determinant of the long-term effectiveness of this procedure.

Mechanisms of symptomatic and functional improvement following endoscopic lung volume reduction

Preliminary results from clinical trials involving some of the methods described earlier are now available, and indicate that these different non-surgical approaches to lung volume reduction may well improve lung function through distinct physiological mechanisms that do not necessarily involve, or require, a reduction in static lung volumes.

Although only a minority of patients treated with endobronchial valves (EBV) have demonstrated measurable reductions in lung volume, presumably because of extensive collateral ventilation within the emphysema lung, a much larger fraction of patients have benefited clinically from the procedure. Six-minute walk distances and walking oximetry saturation values have improved in the majority of studies, suggesting that EBV placement may alter regional time constants for filling and emptying targeted regions of lung. By selectively impeding gas flow into treated areas, these valves can reduce dynamic hyperinflation during exercise, an effect that may not be reflected in changes in spirometry but could improve exercise capacity and ventilation–perfusion matching. Furthermore, although the primary mechanism responsible for improvement in respiratory function following LVRS appears to be relief of restrictive physiology through lung–chest wall resizing, increases in FEV_1 can result from changes in regional expiratory time constants caused by small reductions in the size of overly compliant regions, and concomitant expansion of adjacent less compliant regions. The net effect of such a response could be an overall improvement in FEV_1 without an accompanying

change in RV or RV/TLC. Responses of this type have been observed following EBV therapy. Clearly, more detailed physiological information is required to fully understand the basis for responses to EBV treatment, and is likely to be forthcoming upon completion of ongoing clinical trials.

Early Phase 1 clinical results using tissue engineering BLVR suggest that this approach may produce physiological responses that more closely parallel those of conventional lung volume reduction. Treatment in a limited number of patients has been associated with substantial increases in FEV_1 and FVC, together with reductions in RV and RV/TLC ratio by day 7. These data suggest that, in contrast to EBV therapy, true reductions in lung volume can be achieved using this method, although response durability has not yet been assessed.

Clinical experiences using RFA to create fenestrations are not yet available, although nonclinical studies attest to the physiological soundness of this approach. Clinical trials are ongoing.

Summary

As described earlier, a number of novel, non-surgical approaches for achieving BLVR reduction for treatment of advanced emphysema are currently being developed and evaluated in clinical trials. Endobronchial valve systems (Emphasys Medical Inc. and Spiration Inc.) are the simplest and most direct. Testing in humans has shown these valves to be relatively safe, and it is likely that they will be the first of the non-surgical systems available on the market for widespread use by pulmonologists and interventionalists. Their principal limitation may be the lack of effectiveness due to the inherent design limitation of trying to use an endobronchial blocking device to produce collapse in a disease in which extensive collateral pathways and premature distal airway closure are universal. Nevertheless, preliminary studies suggest that a subset of treated patients may benefit from this approach. Ongoing larger studies will be important to identify appropriate selection criteria for those patients who may benefit.

Use of tissue engineering to remodel, and to shrink damaged areas of lung (Aeris Therapeutics, Inc.) has been shown to produce effective lung volume reduction in nonclinical trials involving large animal models of experimental emphysema. This approach has the appeal of being simple to perform, and its physiological effectiveness is not limited by the presence of collateral ventilation. Early Phase 1 clinical results demonstrate that the procedure is well tolerated and physiologically effective, but long-term safety and effectiveness data are not yet available.

An airway bypass procedure that uses RFA to generate shunt pathways through damaged areas of lung (Broncus Technologies Inc.) is also being evaluated. Nonclinical studies in isolated lungs confirm the scientific soundness of this approach and intraoperative studies suggest that it is feasible. However, the procedure is somewhat complex, and its clinical safety and effectiveness will need to be evaluated in longer-term clinical trials.

Conclusions

Although all of the technologies summarized here have potential benefits as well as limitations, and it is not yet clear how each will function in the clinic, it is apparent that pulmonologists, interventionalists and surgeons will have a variety of new therapies for treatment of emphysema to consider in the next few years. It is likely that at least some of these methods will prove clinically useful, and help reduce the medical and financial burden associated with treating patients with advanced emphysema.

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13 CHAPTER 13

Endobronchial gene therapy

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Gene therapy for pulmonary disease has progressed considerably in the past decade. The technological advances of gene transfer may someday treat a variety of pulmonary disorders, including airway, parenchymal, vascular or pleural processes. There have been significant preclinical developments and several Phase I clinical trials for a variety of respiratory disorders [1]. The flexible bronchoscope, because of its unique access to both large and small airways, serves as an ideal instrument to deliver therapeutic genes to the tracheobronchial tree, even to small airways and alveoli beyond the visual reach of the bronchoscope. Bronchoscopic gene delivery even has the potential of targeting pulmonary vascular disorders [2,3]. At present, however, gene delivery for pleural disorders necessitates access to the chest cavity via tube thoracostomy or thoracoscopy [4].

Modes of delivery

Designing a gene therapy study involves the choice of: a therapeutic gene for transfer (transgene); a target cell; and a suitable method for gene delivery. Most gene transfer protocols involve the use of a "vector" – the mechanism by which genetic material is transferred to the target cell. The most common vectors are viruses such as adenovirus or retrovirus that have adapted over millions of years to pass their genetic cargo to human cells. Liposomes, artificial constructs of lipid, protein and DNA, are good examples of nonviral vector systems that have been implemented in several human gene transfer studies. Vector delivery can be accomplished *ex vivo*, in which autologous cells are removed, genetically modified and then returned to the recipient [5,6], or *in vivo*: directly to the target cells of an individual, via various routes (intravenous, intracavitary, intratumoral, etc.) [7,8].

In studies of pulmonary gene transfer, *in vivo* airway-mediated vector delivery has been the most widely utilized approach. Current limitations in cell delivery technology limit the ability of *ex vivo* gene transfer methods to target broad areas of the pulmonary epithelium. Given the versatility of flexible bronchoscopy for a wide range of diagnostic and therapeutic tracheobronchial procedures, it is the ideal instrument for facilitating intrapulmonary gene transfer.

Currently, there are three primary delivery methods for bronchoscopic gene therapy: (a) *direct instillation* of soluble vector via bronchial/bronchoalveolar lavage (BAL); (b) *aerosolization* of vector via specially designed spray catheters; and (c) *direct injection* of vector via transbronchoscopic needle (TBNI) (Table 13.1). These three methods can be applied for use in varying clinical applications (Table 13.2).

Direct instillation

Gene transfer vectors can be easily delivered through the working channel of a flexible bronchoscope in a manner analogous to a bronchial lavage, with the caveat of vector solution instillation without subsequent aspiration. This approach facilitates directed delivery of vectors into a specific pulmonary segment. Isolation of the targeted segment with a balloon-tipped catheter during instillation can minimize spillover into adjacent regions of the lung. Using this delivery method, therapeutic genes can be administered, in theory, to the entire tracheobronchial tree. Achieving this in practice, however, can be much more difficult. After bronchoscopic instillation, e.g. viral vectors preferentially distribute into the small distal airways and alveolar spaces [9]. For these

Table 13.1 Bronchoscopic methods for gene delivery.

	Instillation	*Injection*
Advantages	Bypasses upper respiratory tract Theoretical delivery to entire tracheobronchial mucosa	Avoids tracheobronchial defenses Highly localized delivery
Disadvantages	Distal delivery to alveoli Poor efficiency due to defense barriers	Limited area of vector administration Potential for systemic dissemination

Table 13.2 Potential applications for bronchoscopic gene therapy.

Local delivery	*Diffuse delivery*
Endobronchial tumor	Carcinoma in situ, "field" carcinogenesis
Granulation tissue/stricture/web	Multifocal bronchioalveolar cell carcinoma
Tracheoesophageal fistula	Cystic fibrosis
Anastamosis dehiscence	Obstructive airway disease (asthma/COPD)
	Alpha-1 anti-trypsin deficiency
	ARDS

reasons, direct instillation may be best utilized in the treatment of diffuse, parenchymal lung diseases, such as idiopathic pulmonary fibrosis or bronchioloalveolar carcinoma.

Spray catheter

For diseases centered in the respiratory epithelium such as cystic fibrosis (CF) or asthma, the more proximal conducting airways are the targeted site – a zone typically bypassed by direct bronchoscopic instillation. More efficient delivery of viral vectors to the conducting airways may be achieved with recently developed transbronchoscopic sprayer devices (MicroSprayer, Penn Century; Philadelphia, PA and Model PW-6p, Olympus, Lake Success, NY) [10–12]. These sprayers, which are introduced through the working channel of a flexible bronchoscope, aerosolize the soluble vector into relatively large particles (10–25 microns), preferentially depositing them in the large conducting airways, and minimizing distal delivery [13].

Spray delivery of gene transfer vectors thereby targets the central airways, in contrast to nebulized vector delivery, which generates small aerosol particles (typically 1–5 microns in diameter) capable of dispersing to the smaller airways and alveoli. Although vector aerosolization via nebulizers offers a simple, noninvasive means of gene delivery to the lung parenchyma, the nebulization process may have deleterious effects upon vector viability. Vector damage can occur as a result of thermal injury from heat generated during ultrasonic nebulization, or from mechanical injury related to the baffles used to dissociate the carrier fluid during aerosol generation [14].

Aerosol gene therapy delivery necessitates usage of higher vector titers as a significant proportion of the vector dose never reaches the lower airways. Additionally, this excess vector deposited in the upper airway (naso-, oropharynx), can elicit both local and systemic side effects. In contrast, bronchoscopic gene delivery bypasses the upper airway completely, minimizing the total amount of vector needed, potentially translating into significant safety and cost benefits.

Unfortunately, there have been significant obstacles to successful therapeutic gene delivery with both bronchoscopic instillation and aerosolization techniques. Intrapulmonary gene transfer with soluble vectors in humans has been quite inefficient, in part secondary to the innate defense mechanisms of the tracheobronchial epithelium [15]. Specifically, the mucous barrier

and normal mucociliary clearance serve to impair successful transduction of bronchial epithelial cells and submucosal glands. To be successful, most gene therapy approaches require transduction of a significant proportion of target cells. This is difficult with current techniques of instillation or aerosolization of soluble vectors; however, a variety of approaches are being tested to overcome these barriers (see "Future directions").

Direct injection

Direct vector injection via TBNI is a rational approach for the treatment of endobronchial lesions and peribronchial masses, particularly bronchogenic malignancies (Table 13.2). One advantage of this method is that it bypasses the potent host defense mechanisms of the airway mucosa. Furthermore, direct intratumoral injection may confine vector delivery to the injected area, mitigating systemic spread of the vector, and thereby potential toxicity. Unfortunately, larger endobronchial tumors may require multiple vector injections, potentially increasing procedure time, patient discomfort and risk of systemic dissemination. The risks of this mode of gene delivery may be diminished in the future by use of real-time ultrasound guidance (EBUS-FNA).

Bronchoscopic delivery of gene therapy: clinical trials

There are numerous potential applications for gene therapy in the treatment of a variety of pulmonary disorders [1]. A number of investigators have pursued *in vivo* gene therapy studies targeting the pulmonary parenchyma, airways, vasculature and pleural space. Several studies of bronchoscopic delivery of therapeutic genes in humans have already been completed, primarily in two prevalent pulmonary diseases with significant morbidity and mortality: CF and non-small cell lung cancer (NSCLC).

Cystic fibrosis

Cystic fibrosis is a common genetic disease associated with abnormalities in a transmembrane chloride channel: the CF transmembrane conductance regulator (CFTR). Phenotypic chloride channel dysfunction is the result of one or more mutations in the CFTR gene [16]. The mutated CFTR prevents the normal movement of fluid and electrolytes across various epithelial cellular membranes. In the lungs, this defect in electrolyte trafficking results in increased viscosity of secretions, impairment of mucous clearance and weakening of local host defenses [17,18]. In combination, these abnormalities engender repeated bouts of infection and inflammation resulting in marked pulmonary destruction. In fact, upward of 90% of CF patients eventually succumb to respiratory complications [19].

Since the realization that CFTR mutations were the predominant genetic abnormality in CF, many investigators have sought to supplant the mutant gene with a normally functioning "wild-type" (wt) copy. Early *in vitro* studies indicated that expression of wt CFTR in as few as 6–10% of mutant cells could normalize chloride transport [20,21]. Based upon these findings, there was much enthusiasm in the scientific community that gene therapy for CF would lead to a "cure" for the disease.

In human CF gene therapy clinical trials, three vector systems, adenovirus (Ad), adeno-associated virus (AAV) and lipid/DNA complexes (liposomes) have been utilized to deliver wt CFTR to the respiratory epithelium. Of these, adenovirus has been the most commonly utilized vector. To date, seven clinical trials involving adenoviral-mediated CFTR (Ad.CFTR) transgene delivery have been reported, four of which employed bronchoscopic instillation.

Crystal and colleagues at Weill Medical College of Cornell University performed the first human study of bronchoscopic instillation of Ad.CFTR into the lower airways [22]. In this dose-escalation study, Ad.CFTR was administered to the nasal and respiratory epithelium. In four patients, soluble adenovirus (5–20 cc) was directly instilled via the working channel of a flexible bronchoscope into the segmental airways of a specified lobe. This Phase I trial of CFTR gene transfer was, in general, well tolerated. In some of the patients, there was evidence of successful gene transfer to the bronchial epithelium determined by wt CFTR expression in a number of the post-treatment specimens. One of the four patients enrolled developed fevers, hypotension and pulmonary infiltrates after bronchoscopic delivery of 2×10^9 plaque forming

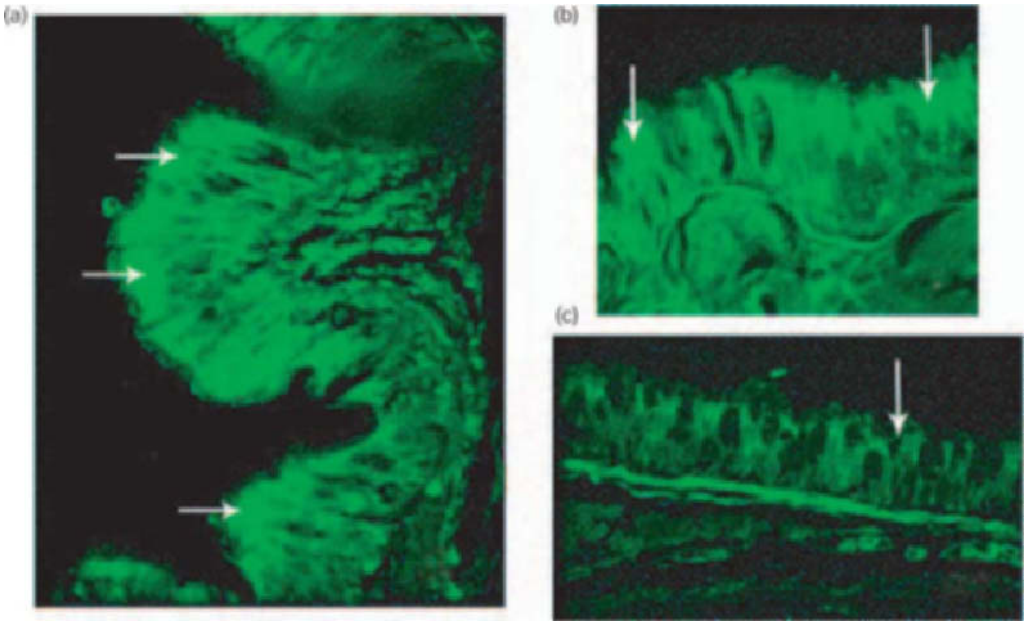

Figure 13.1 Adeno-associated virus (AAV) bronchoscopic gene delivery. (a)–(b) Green fluorescent protein (GFP) expression in bronchial epithelium analyzed by confocal microscopy (400×) in macaques treated with AAV2-GFP via bronchoscopic aerosolization. (c) Absence of GFP-specific expression in pulmonary sections from a control macaque. Reproduced from [28] with permission.

units (pfu) of the Ad.CFTR vector, with complete resolution of the toxicity within 30 days of vector instillation [22].

Subsequently, investigators at the University of Pennsylvania Medical Center conducted a Phase I clinical trial in 11 patients with CF utilizing a putatively less immunogenic Ad.CFTR vector deleted in the early adenoviral genes E1 and E4 [23]. This "third generation" Ad.CFTR vector was instilled bronchoscopically into the conducting airways, preferentially segments without significant distal bronchiectasis or mucoid impaction. The investigators were able to demonstrate successful, albeit inefficient, wt CFTR gene transfer into bronchial epithelial cells. CFTR transfection was detected in less than 1% of bronchial epithelial cells at 4 days after vector administration, and was not detectable at all at 42 days. The most common side effect seen on patients at all dose levels was a flu-like complex comprising fatigue, headache, nausea and myalgias. Dose-limiting toxicity manifested by high fevers and persistent pulmonary infiltrates was noted in several patients at a dose level 1×10^{11} viral particles [23].

An additional 20 patients underwent bronchoscopic instillation of Ad.CFTR in a subsequent Phase I study designed to assess gene transfer safety and efficacy [24]. In general, vector administration was well tolerated; however, several patients developed a cough, and one had mild hemoptysis. Additionally, four patients evolved radiographic infiltrates following vector administration, although none had associated significant oxyhemoglobin desaturations. Transduction efficiency with topical instillation of Ad.CFTR was quite low, and the vast majority of successfully transduced cells did not appear to be of epithelial origin. Overall, at most vector doses, less than 1% of the airway epithelial cells were effectively transduced [25].

Adeno-associated virus has been advocated as a superior vector for delivery of wt CFTR to the bronchial epithelium. Theoretical advantages of AAV over Ad as gene therapy vectors include: prolonged transgene expression; and decreased vector-induced inflammatory responses (Figure 13.1) [26–28]. Researchers at the University of Florida reported the results of the first Phase I study of

bronchoscopic AAV.CFTR gene delivery in 25 adult and adolescent CF patients with mild–moderate lung disease [29]. To date there have been no serious toxicities noted other than minimal pulmonary inflammation [14]. More recently, University of Florida investigators described a second Phase I trial involving aerosol delivery of AAV.CFTR in 12 patients with mild CF [30]. This study demonstrated that aerosolized AAV.CFTR was safe with minimal side effects. The presence of wt CFTR DNA was detectable in bronchial epithelium for up to 30 days following treatment via polymerase chain reaction (PCR) techniques; however, there was no evidence of wt CFTR RNA expression on reverse-transcriptase PCR (RT-PCR) analysis [30].

Liposome/wt CFTR complexes have also been utilized as delivery vectors in CF gene therapy clinical trials, including several studies involving topical delivery to the nasal mucosa, and intrapulmonary aerosolization. Both methods of vector delivery facilitated successful transduction of the respiratory epithelium [31]. Toxicities related to aerosol delivery of liposomal/wt CFTR DNA complexes included: fevers; myalgias and arthralgias attributable to inflammatory responses against the liposomal/DNA complexes. Repeated aerosol delivery of lipid/DNA complexes into the airways might, therefore, elicit significant inflammatory responses that inhibit CFTR gene expression in the airway epithelium. Liposomal vectors, however, have yet to be delivered to humans via bronchoscopy [31].

In summary, the human clinical trials to date have demonstrated successful bronchoscopic CFTR gene transfer to the tracheobronchial epithelium in some studies, albeit with low-level gene expression. For CF gene therapy to become a therapeutic reality, however, efficiency of tracheobronchial transduction will require significant improvement.

One novel approach to achieve improved transduction efficiency in CF involves delivery of wt CFTR *in utero*, before expression of the CF phenotype can engender lung destruction. Intra-amniotic injection of gene transfer vectors in animals has been demonstrated to successfully deliver reporter genes to the pulmonary epithelium [32,33]. In addition, *in utero* bronchoscopy has been used for delivery of an adenoviral vector carrying the beta-galactosidase reporter gene in fetal sheep with no evidence of acute toxicity [34]. Marker gene expression was demonstrated in the pulmonary parenchyma, particularly the type II pneumocytes, but absent in the large conducting airways [34]. This *in utero* gene transfer technique could potentially be utilized in humans to treat congenital pulmonary diseases such as alpha-1 antitrypsin deficiency and surfactant protein B deficiency.

Non-small cell lung carcinoma

Other than CF, NSCLC represents the other major pulmonary disease category targeted in bronchoscopic gene transfer clinical trials [35]. The focus to date has been on the treatment of endobronchial NSCLC and bronchioloalveolar cell carcinoma (BAC). The bronchoscopic gene therapy strategies studied for NSCLC investigated to date range from injection of wt tumor suppressor genes to intratumoral delivery of immunostimulatory genes.

Replacement of tumor suppressor genes

A common gene therapy strategy used for NSCLC involves supplementation of mutated or absent tumor suppressor genes with a normal (wt) copy of the gene. The rationale of this approach is that correction of the molecular aberrancy should reverse the malignant phenotype and thereby restore normal cellular growth and differentiation. The majority of clinical studies have focused on the delivery of wt p53, a tumor suppressor gene that is responsible, among myriad other cellular functions, for detecting and repairing damaged DNA [36]. The wt p53 gene, often referred to as the "guardian of the genome," has multiple tumor inhibitory properties; mutation or loss of p53 predisposes to malignant transformation. Approximately 70% of NSCLC patients harbor mutations and/or deletions in the p53 gene [36–39]. This discovery ultimately led to the initiation of trials of bronchoscopic wt p53 delivery to endoluminal NSCLC tumors.

Intracellular insertion of wt p53 has resulted in NSCLC regression *in vitro* and in animal models of NSCLC [40]. The antitumor effect seen *in vitro* with restoration of wt p53 is a result of tumor cell growth inhibition and the induction of tumor apoptosis. *In vivo*, wt p53 gene therapy shows evidence of a " bystander" effect – the killing of

neighboring, nongenetically modified tumor cells. This *in vivo* p53 bystander effect has been attributed to angiogenesis inhibition, activation of the Fas/Fas ligand system and/or induction of antitumoral immune responses [41–43].

To date, seven wt p53 gene transfer clinical trials for NSCLC have been reported in the medical literature. In most of the patients enrolled in these studies, viral vectors encoding wt p53 were bronchoscopically injected into endobronchial tumors. In the first reported trial, conducted at the M.D. Anderson Cancer Center in Houston by Roth and colleagues, a retroviral vector was used to deliver wt p53 in nine patients with advanced, treatment-refractory NSCLC, via bronchoscopic injection (four) or transthoracic needle injection (five) into endobronchial or parenchymal tumors, respectively [44]. Overall this gene transfer approach was well tolerated with minimal side effects, and with successful transgene expression and induction of apoptosis. Three of the patients who received bronchoscopic p53 gene delivery demonstrated local tumor regression at the injection site. Ultimately, all of the patients in this initial trial died of progressive disease at distant untreated sites [44].

All subsequent trials of wt p53 gene transfer for NSCLC have utilized Ad vectors, in part due to the difficulties involved in production of large quantities of retroviral vectors. In general, endobronchial delivery of Ad.wt p53 vectors has been well-tolerated and associated with tolerable side effects, most commonly a flu-like syndrome characterized by fevers, chills and fatigue. Both single and multiple injection schedules have been assessed in clinical trials, with the goal of increasing the degree and duration of transgene expression [45,46]. These trials demonstrated successful dose-related intratumoral gene transfer; however, the use of multiple doses engendered increased titers of anti-adenoviral antibodies [47]. As with the prior retroviral trial, local responses were seen in about 50% of patients; however, there was no evidence of antitumor effect at metastatic sites.

Subsequent human trials combined bronchoscopic Ad.wt p53 gene delivery with conventional chemotherapy, based upon the hypothesis that increased intratumoral expression of wt p53 will enhance apoptosis induced by DNA-damaging agents such as chemotherapeutic drugs and ionizing radiation [48]. In one of these studies, patients treated with cisplatin followed by bronchoscopic injection of Ad.p53 demonstrated increased tumor responses compared with those receiving p53 gene transfer alone (Figure 13.2). Specifically, only one of five patients treated with Ad.p53 alone achieved relief of endobronchial obstruction compared with five of seven patients treated with cisplatin and Ad.p53 [49].

In a subsequent European study, chemotherapy-naive patients with advanced NSCLC were randomized to receive standard chemotherapy with either cisplatin and vinorelbine or carboplatin and paclitaxel in combination with endobronchial injection of Ad.p53 [50]. Despite evidence of successful intratumoral gene transfer, there was no *overall* difference in tumor response rate or survival of patients treated with chemotherapy plus Ad.p53 (52%) versus chemotherapy alone (48%). There were response differences seen in those patients receiving the "less effective" chemotherapy regimen (cisplatin and vinorelbine). In these patients, the addition of Ad.p53 gene transfer to chemotherapy significantly improved tumor response rates [50].

In another trial, external beam radiation therapy (EBRT) was combined with bronchoscopic Ad.p53 intra-tumoral gene delivery (days 1, 18 and 32) in patients with locally advanced NSCLC [51]. Patients enrolled in this study were deemed ineligible for conventional chemoradiotherapy or surgical resection due to significant comorbidities, including poor pulmonary function. Overall, this protocol was well tolerated with minimal toxicity. Sixty percent of patients had either a partial or complete response at the treatment site 3 months following the completion of Ad.p53 and EBRT (Figure 13.3). Furthermore, in 63% of patients in the clinical trial, biopsy of the injection site at 3 months revealed no evidence of residual tumor. This response rate is higher than that of historical controls with locally advanced NSCLC treated with EBRT alone, supporting the hypothesis that increased wt p53 expression fosters the sensitivity of tumor cells to ionizing radiation [52].

Unfortunately, many patients in this trial developed metastatic tumor, consistent with the notion that p53 gene transfer may be effective at providing loco-regional responses, but not distant control of

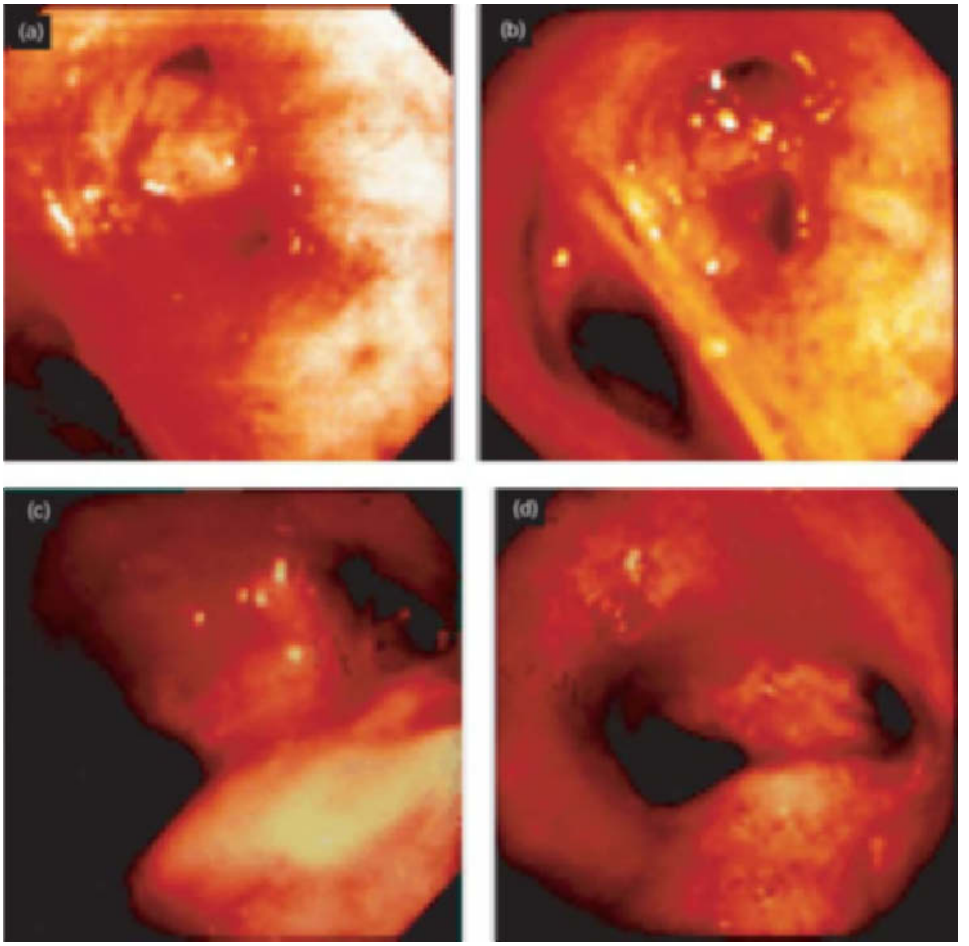

Figure 13.2 Tumor response status post endobronchial Ad.wt p53 injection followed by systemic administration of cisplatin in Patient 26 ([a] and [b], pre- and post) and Patient 49 ([c] and [d], pre- and post). Reproduced from [48] with permission.

disease. Additional Phase III trials of intratumoral Ad.p53 injection, in combination with chemo-radiotherapy, are underway to determine whether improvement in loco-regional control translates into benefits in survival and/or quality of life.

Bronchioloalveolar cell carcinoma

Bronchoscopic delivery of Ad.p53 has also been studied in patients with advanced, refractory BAC [53]. Lobar or multifocal BACs represent a subset of NSCLC that are not often surgically curable, and are resistant to conventional chemotherapy and radiation therapy [54–56]. BAC is an ideal tumor target for bronchoscopic gene therapy, because of the pathologic structure of the cancer involving thin layers of tumor cells lining the alveolar walls and distal bronchioles.

For this reason, the Eastern Cooperative Oncology Group conducted a Phase I dose-escalation trial of Ad.wt p53 in BAC (ECOG E6597) in which vector was delivered to affected lobes by BAL. Patients underwent serial administrations of Ad.p53, with a maximum in this study of 14 separate doses. Overall, bronchoscopic delivery of Ad.p53 in BAC patients was well tolerated, although one patient did develop grade 4 pulmonary toxicity. Of the 9 evaluable

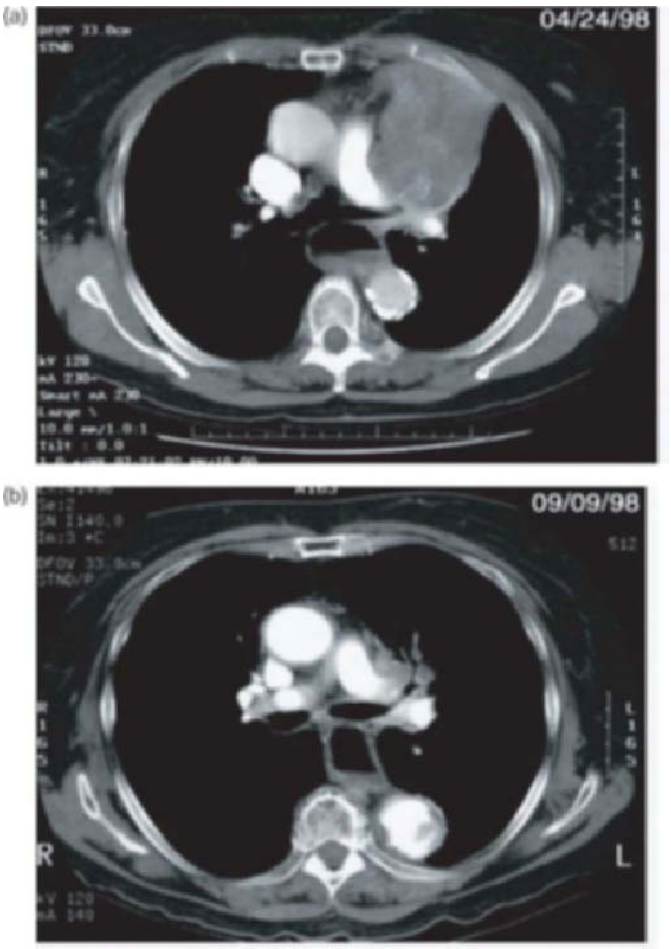

Figure 13.3 Endobronchial Ad.wt p53 injection and radiation therapy. (a) Baseline chest CT scan of Patient 2 who had a respectable left upper lobe mass. Patient 2 received three bronchoscopic injections of Ad.p53 (3×10^{11} vp) in combination with radiation theraphy (60 Gy). (b) Repeat CT chest scan 3 months after completion of therapy. Pathologic biopsies obtained at that time were negative for viable tumor. Reproduced from [51] with permission.

patients in this noncontrolled study, 4 had symptomatic improvement, 4 had increases in their diffusion capacity and 2 had pathological responses confirmed on bronchoscopic lung biopsy [53].

Additional studies are ongoing to more formally assess the effectiveness of Ad.p53 gene therapy for BAC, both alone and in combination with systemic chemotherapy.

Genetic immunotherapy

Another novel bronchoscopic approach for treating NSCLC and other thoracic malignancies involves delivery of therapeutic genes designed to enhance local and systemic antitumor immune responses [57]. In the mid-1990s, French investigators conducted a Phase I dose-escalation clinical trial of bronchoscopic injection of an adenoviral vector containing the *Escherichia coli* gene *lacZ* (which encodes for the enzyme, beta-galactosidase [β-gal]) into endobronchial NSCLC [58–59]. Overall, bronchoscopic Ad.lacZ injection was well tolerated, except for fever and minor injection site bleeding. The investigators demonstrated β-gal expression in targeted tumor cells, as well as induction of both anti-adenoviral and anti-β-gal immune responses. In addition, localized tumor responses were observed at the injection site, putatively due to induction of immune responses directed against the tumor cells expressing the foreign β-gal protein. Several laboratories are currently studying

novel gene therapy vectors that deliver transgenes (i.e. cytokine genes) designed to more effectively stimulate antitumor immunity [60].

Preclinical trials of novel endobronchial gene therapy approaches

In addition to ongoing endeavors for CF and NSCLC, bronchoscopic gene therapies are currently in development for several other pulmonary diseases. For many of these disorders, these preclinical studies may ultimately lead to human clinical trials. One disease candidate, an early target of preclinical gene therapy experiments, is alpha-1 anti-trypsin deficiency (A-1AT). This autosomal recessive disease, characterized by pan-acinar emphysema and hepatic cirrhosis, results from a deficiency of the anti-protease A-1AT [61]. Normalization of serum A-1AT levels can forestall disease progression; and levels as low as 11 units/μL may be sufficient to protect the lungs from excessive protease activity. Several attempts have been made to replace the A-1AT gene in the airway and alveolar epithelium in animal models. Unfortunately, *in vivo* gene therapy experiments involving systemic or endobronchial delivery of the A-1AT gene have only resulted in transient low-level increases in A-1AT levels [62,63].

Asthma is another potential disease target for bronchoscopic gene therapy approaches. Intrabronchial delivery of therapeutic genes, in particular those encoding for Th1-type cytokines such as interleukin-12 or interferon-gamma, in animal models of asthma has been shown to decrease airway hyperreactivity [64–66]. Given the relative safety and efficacy of standard asthma therapeutics, bronchoscopic gene therapy may find a role as an adjunctive treatment in patients with severe steroid-dependent disease.

Inflammatory pulmonary conditions such as radiation pneumonitis and the adult respiratory distress syndrome (ARDS) have also been the target of gene therapy approaches, most notably intrabronchial delivery of antioxidant genes. In one study, Danel and colleagues delivered adenoviral vectors encoding superoxide dismutase (SODM) intra-tracheally in a murine model of oxidative lung injury [67]. In another preclinical study, Epperly and coworkers demonstrated that intra-tracheal delivery of the SODM gene reduced fibrosis and alveolitis in gamma-irradiated mice [68].

The list of potential applications for bronchoscopic delivery of therapeutic genes is extensive. Surfactant gene therapy (airway delivery of genes encoding for surfactant proteins) is being investigated for the treatment of neonatal respiratory distress syndrome and other related surfactant deficiency states [69,70]. Several groups are assessing the role of immuno-suppressive gene therapy to prevent lung transplant rejection [71]. Experimental antifibrotic gene therapy approaches are being studied in animal models of interstitial lung diseases [72,73]. Bronchoscopic delivery of antimicrobial gene therapy may someday aide the immune system in eliminating and destroying a variety of human pathogens including bacteria [74–77], mycobacteria [78], virus [79], fungi [80] and pneumocystis [81].

Future directions

Although bronchoscopic gene delivery will likely hold an important place in the future therapeutic armamentarium of pulmonary diseases, currently available vectors need to be made safer and more efficacious prior to large-scale usage. The major obstacles for bronchoscopic gene therapy remain inefficient transduction and vector-related toxicities. Human clinical trial experience, accumulated over the past decade, supports the general safety of this technology, and recently the State Food and Drug Administration (SFDA) in China approved the clinical use of Ad.wtp53 for refractory head and neck carcinoma (Figure 13.4) [82]. Nonetheless, the development of acute lung injury, noted in some patients in the CF and BAC trials, is of concern, and a potential limitation to widespread human application. This toxicity was attributed to the distal intra-alveolar delivery of adenoviral vectors with resultant induction of innate inflammatory responses. As a result, many investigators are in the process of developing novel bronchoscopic delivery methods to facilitate localized gene delivery to the large conducting airways, including sprayer devices and gene-coated endobronchial

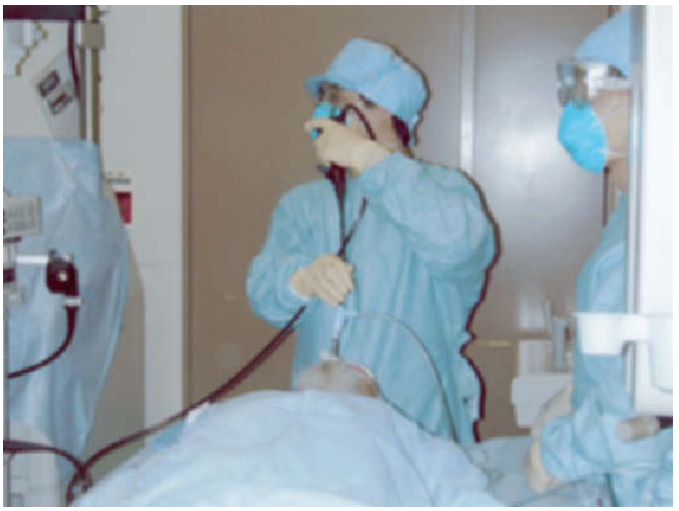

Figure 13.4 Endobronchial gene therapy around the world. Investigators in many countries on several continents are studying a veriety of approaches to bronchoscopic gene therapy. Pictured here is a clinician–scientist from Japan performing bronchoscopic gene vector injection in an intubated patient. The Chinese have just approved Ad.wt p53 gene therapy for clinical use. (Gendicine®, Shenzhen SiBiono Gene Technologies Co. Ltd, Shanghai, China.)

stents. Alternatively, other therapeutic options could include co-administration of antioxidant genes such as SODM to decrease vector-mediated inflammatory responses.

Investigators are also evaluating novel technologies to improve the transduction efficiency of bronchoscopic gene delivery. For example, co-administration of Ad vectors with surfactant [83,84], or after DNAse treatment [85,86] can enhance gene expression. Other strategies aim to increase vector access to target cells, such as the use of calcium chelators (i.e. EDTA) to disrupt the tight junctions [87–89], or polycations to aid in the internalization of gene therapy vectors [90–92].

Another experimental approach to improve transduction efficiency of bronchoscopic gene delivery is to increase the contact time between the airway epithelium and the vector [93]. Thixotropic solutions, such as carboxymethyl cellulose, can reversibly impair mucociliary clearance [94], and thereby prolong contact time between vector and target cells. Stent-mediated gene delivery may also prolong vector–target cell contact, and engender improved transduction efficiency [95].

Real-time bronchoscopic detection of airway transgene expression may facilitate minimally invasive evaluation of gene transfer efficacy and duration. Experimental approaches for this concept involve bronchoscopic delivery of bivalent vectors carrying a therapeutic transgene as well as the reporter gene green fluorescent protein (GFP). Subsequent fiberoptic bronchoscopy with incorporation of specially designed fluorescent filters can detect GFP expression *in situ* within the tracheobronchial epithelium. Flotte and colleagues at the University of Florida used such a device to detect AAV- and Ad-vector mediated GFP expression within the bronchial epithelium of New Zealand white rabbits [96].

Ultimately, the ability to facilitate and monitor gene transfer efficacy will be critical for actualization of the full therapeutic potential of bronchoscopic gene therapy. One important by-product of enhanced transduction efficiency would be improved safety and lowered cost, as less vector would be required per patient treatment [90–92]. Achievement of these goals should help advance bronchoscopic gene therapy from science fiction into standard clinical practice.

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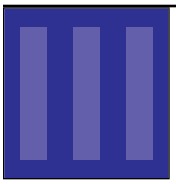

PART III

Interventional pleurology

14 CHAPTER 14

Thoracentesis, percutaneous needle biopsy of pleura, small-bore catheter drainage: does size really matter?

Luis Miguel Seijo, MD

Clinical significance of pleural effusions

Physiology of pleural effusions

The pleural cavity is a potential anatomic space which acts normally as a transit hub for pleural fluid. While no reliable data exist on the amount of pleural fluid present in the pleural space of humans, it is unlikely to exceed several milliliters at any given time. A pleural effusion occurs when the homeostatic mechanisms which control transit of pleural fluid across this potential space are disrupted. Common etiologies leading to the abnormal accumulation of pleural fluid include increased interstitial fluid in the lung parenchyma, increased intravascular pressure within the pleura, increased protein in the pleural space, decreased intrapleural pressure and impaired pleural fluid absorption [1].

Generally speaking, a pleural effusion imposes a restrictive ventilatory defect on the patient, and may adversely affect diaphragmatic function as well as cardiac output [1,2]. However, the diagnostic and therapeutic implications a pleural effusion may have for a given patient depend on a variety of factors including: whether the effusion is an exudate or a transudate, the presence or absence of infection or significant amounts of blood in the pleural cavity, the quantity of pleural fluid and the overall cardiac and respiratory status of the patient.

Physiologic implications of thoracentesis

Drainage of pleural fluid, particularly in the case of massive effusions, may benefit the patient by providing immediate symptomatic relief, invaluable diagnostic information, as well as improvements in respiratory muscle function and cardiac output. Improvements following therapeutic thoracentesis seem to be more pronounced in patients with high pleural pressures [3]. However, while some authors have reported reliable improvements in PaO_2 following thoracentesis, ostensibly due to improvements in the physiologic shunt [4], others have noted that oxygenation may deteriorate initially as a result of thoracentesis [5,6], In addition, exercise tolerance following therapeutic thoracentesis may not improve significantly in patients with pleural effusions [7]. Therefore, careful consideration of each patient's individual presentation should always guide the clinician in deciding whether a procedure is indicated, and if so, whether to proceed with diagnostic and/or therapeutic thoracentesis, or if a more invasive tube thoracostomy is warranted.

Thoracentesis

Indications

All pleural effusions are pathological in the sense that they never occur in the absence of disease. Therefore, diagnostic sampling of pleural fluid is indicated in most cases of pleural effusion, particularly when an etiology is not readily apparent. When the cause of a given pleural effusion is already known, thoracentesis may be helpful in monitoring the patient's response to a given intervention [8,9]. In addition, therapeutic thoracentesis may be indicated in order to provide symptomatic relief when a large pleural effusion is suspected to be the cause of dyspnea.

In order to proceed with thoracentesis, pleural fluid should be accessible, and the quantity of it sufficient to ensure success (most clinicians consider 1 cm of layering on a decubitus film adequate). Some indications for thoracentesis are relatively urgent, such as is the case when the presence of infection or blood is suspected in the pleural space, or when the size of a pleural effusion compromises normal cardiopulmonary function. Other clinical scenarios suggest caution including: an unusual distribution of pleural fluid, the absence of layering on a decubitus chest radiograph or deviation of the trachea toward the affected side to name a few. Such findings may indicate the presence of trapped lung physiology, atelectasis or a thickened pleural space, which might either complicate or contraindicate thoracentesis.

Contraindications

Strictly speaking, there are very few contraindications to diagnostic thoracentesis. Perhaps the most significant concern when performing the procedure is the risk of significant bleeding in those patients who are anticoagulated or suffering from a bleeding disorder, either congenital or acquired. We routinely perform diagnostic thoracentesis in patients with an International Normalization Ratio (INR) of 2 or less, while platelet counts of 25 000/mm^3 or more have been reported as consistent with minimal bleeding following this benign procedure [10]. Indeed, patients with mild coagulation abnormalities do not appear to be at increased risk of bleeding [10].

Although this might seem obvious to the experienced practitioner, it is imperative to be as certain as possible, with ultrasound confirmation if necessary, that an opacification on a chest radiograph represents pleural fluid. Patients with atelectasis or pleural fibrosis, both of which might be mistaken for pleural fluid, should not undergo thoracentesis. Also, thoracentesis in patients with pleural effusions related to a malignant central airway obstruction should be managed cautiously, as drainage of pleural fluid in this clinical scenario may be uncomfortable and fruitless, if not a disservice to the patient. Finally, thoracentesis should be postponed in those patients whose skin at the puncture site is infected posing a serious obstacle to the maintenance of a sterile field throughout the procedure.

Technique

Proper technique is essential in order to ensure success and prevent complications. A safe thoracentesis relies heavily on the availability of adequate equipment, thoughtful preparation and the practitioner's skill. A careful physical examination is always helpful in determining whether an opacity on a chest radiograph represents an abnormal accumulation of pleural fluid or something else, and in choosing the puncture site. Whenever possible, chest radiographs including lateral decubitus views should be obtained prior to the procedure. Occasionally, ultrasound is performed in order to mark the optimal site for thoracentesis. This is sometimes necessary when the presence of loculated fluid is known or suspected, the pleural effusion is small or anteriorly located, or when a previous attempt at "blind" thoracentesis has failed [11]. Although, at least one randomized study found only a slight difference between ultrasound guided thoracentesis, and thoracentesis following decubitus chest radiographs [12], other authors have found distinctive advantages to ultrasound guided thoracentesis, particularly in reducing the number and severity of complications (reductions in the incidence of post-procedure pneumothorax from 18 to 3% have been reported) [13,14]. Whenever an ultrasound is obtained, thoracentesis should be carried out immediately, thus avoiding repositioning of the patient or fluid shifts that would render

the information provided by the ultrasonographer useless or misleading.

Care should be taken to correct any coagulopathy which might otherwise lead to excessive bleeding. The patient should be informed of the risks and made as comfortable as possible, and all of the necessary equipment for a successful thoracentesis should be assembled at the bedside. Adequate preparation for all contingencies minimizes delays and interruptions which might lead to patient discomfort or disruption of the sterile field. While thoracentesis is quite safe, serious complications can take place, such as hypoxemia or pneumothorax [6]. The clinician should make sure that the appropriate materials to cope with such complications be readily available including chest tubes and oxygen delivery devices, in order to minimize morbidity.

The puncture site for thoracentesis is determined by physical examination of the chest with the patient sitting upright, and the bed elevated. The site should always be above the rib and never below in order to avoid damage to the underlying neurovascular bundle. Proper positioning of the patient is essential in order to facilitate access to the puncture site, avoid shifting of the pleural fluid and minimize discomfort both to the patient and the clinician. Methodical anesthesia of the skin, rib periosteum and the pleural surface is of the utmost importance during the procedure. Preventing pain ensures the patient's collaboration and well-being. Obviously, sterile conditions should be maintained at all times.

A small caliber needle is used initially for superficial anesthesia (usually 22 gauge), followed by a larger bore needle (19 gauge) which facilitates anesthesia of deeper structures including the parietal pleura, and confirmation of the presence of pleural fluid. In most cases, fluid is withdrawn with a 60 cc syringe and sent for whatever studies are deemed necessary by the clinician (see Table 14.1). We send pleural fluid to the laboratory in the containers provided in most commercially available kits, with the exception of the time-sensitive pH measurement which can be sent in a special syringe designed for arterial blood gas analysis. Although this appears to be common practice, a recent study disputes it, suggesting that pleural fluid pH measurements are not altered by exposure to room temperature for as long as an hour following the procedure [15]. We do not recommend pH paper measurements as they appear to be unreliable [16]. Finally, if the fluid is visibly purulent pH measurements are unnecessary.

Following withdrawal of the desired amount of pleural fluid for routine and special studies, one can terminate the procedure unless therapeutic thoracentesis is contemplated. In that case, an introducer needle baring a semi-rigid catheter is advanced into the pleural space through a small skin incision. The introducer needle is carefully withdrawn as the catheter is advanced in order to prevent damage to the expanding lung. The catheter should never be retracted back into the needle in order to avoid its shearing by the needle tip [17], but may be gently repositioned in order to facilitate removal of pleural fluid. Large amounts of fluid can be withdrawn rapidly with the aid of vacuum bottles. Such bottles can then be sent to the cytology laboratory in order to maximize cellular yield when a malignant effusion is suspected or otherwise discarded. Some studies suggest, however, that the volume of fluid sent for cytology has no bearing on diagnostic yield [18].

In general, no more than 1–1.5 L of pleural fluid should be removed from the chest, particularly when dealing with a longstanding pleural effusion, in order to prevent reexpansion pulmonary edema [19]. Persistent coughing during thoracentesis should always be seen as a sign of caution, and if present, often prompts withdrawal of the needle or catheter, and termination of the procedure.

Following successful thoracentesis, whether diagnostic or therapeutic, a chest radiograph is often obtained in order to confirm the absence of a pneumothorax and the presence of adequate lung reexpansion. Routine chest radiography following thoracentesis in the absence of a heightened level of clinical suspicion, however, is not absolutely necessary [20]. In fact, one study found that as many as 60% of chest radiographs following routine thoracentesis were unnecessary based on clinical grounds alone [21]. More importantly, post-procedure care should ensure proper dressing of the puncture site, careful disposal of needles and scalpel and brief monitoring of the patient's oxygenation and vital signs. The onset of dyspnea post-procedure, hypoxemia, hypotension or tachycardia

Table 14.1 Pleural fluid analysis.

Fluid pH	Low in a variety of disorders including parapneumonic effusion, esophageal rupture, malignancy, hemothorax, collagen vascular disease, etc. Levels <7.00 suggest need for chest tube in complicated parapneumonic effusions.
Fluid glucose	Low levels (<60 mg/dL) are consistent with parapneumonic effusion, tuberculosis, rheumatoid arthritis or malignancy.
Fluid LDH	Higher levels are found in exudates. Ratio consistent with exudate is fluid LDH/serum LDH>0.6.
Fluid protein	Higher levels are found in exudates. Ratio consistent with exudate is fluid protein/serum protein >0.5.
Fluid lipids	Triglyceride levels >100 mg/dL consistent with chylothorax, levels <100 mg/dL but >50 mg/dL are inconclusive. Levels <50 mg/dL rule out this diagnosis.
Fluid ADA	Levels >70 U/L are consistent with tuberculosis. Empyemas may also have elevated levels of this enzyme.
Fluid amylase	Elevated levels of this enzyme in pleural fluid are consistent with malignancy, pancreatic tumors and esophageal rupture.
Fluid RBC count	Effusion is a hemothorax if hematocrit is >50%. "Bloody" effusions have RBC >100 000/mm^3 and are typical of malignancy, trauma or pulmonary embolism.
Fluid WBC count and differential	Absolute WBC is rarely useful. Differential may give valuable clues as to the etiology of the effusion.
Fluid cytokines	Interleukin levels at present not useful for diagnostic purposes. γ interferon levels may be useful in tuberculosis.

should be taken very seriously, and prompt a thorough evaluation of potential complications such as pneumothorax or re-expansion pulmonary edema.

Complications

The most common serious complication attributable to thoracentesis is pneumothorax which has been reported in 3–20% of patients undergoing this procedure [14,22]. Factors that may be associated with an increased risk of pneumothorax include aspiration of air during thoracentesis, number of passes with the needle, a history of thoracic radiation and a heightened clinical suspicion [21]. Other authors have noted that the risk of pneumothorax increases when large amounts of fluid are withdrawn and with the use of large bore needles [14]. At least one large study, however, found no reliable indicator of risk [23].

Pneumothoraces may occur for one of two reasons. Essentially, air can rush in from the outside during the procedure as a consequence of the negative pressure existing within the pleural cavity, or it might fill the pleural space from within due to inadvertent puncturing of the lung itself. Whatever the cause, most of these pneumothoraces can be managed conservatively, and a majority of patients do not require chest tube placement [22,24].

Mechanically ventilated patients and patients with chronic obstructive lung disease (COPD) are of particular interest, as they may be at increased risk from complications of thoracentesis [25,26]. The increased risk of pneumothorax in the former patient population has been reported as statistically significant by some authors [27], although others have found the incidence of pneumothorax in mechanically ventilated patients to be a respectable 6–10% [25,28,29]. Ultrasound guidance may be particularly helpful in this clinical setting [30]. The incidence of pneumothorax in patients with COPD following thoracentesis has been reported to be as high as 41.7% [26], mandating careful

monitoring post-procedure. Rare complications following thoracentesis include hemothorax due to laceration of an intercostal artery, splenic or hepatic perforation, intrahepatic arterial aneurysm, catheter fracture, infection of the pleural space and reexpansion pulmonary edema [17,31,32]. The latter may be more common in younger patients undergoing thoracentesis [31]. Cough and pain at the puncture site are common yet minor side effects associated with the procedure [33].

Pleural biopsy

Closed pleural biopsy can be an important adjunct to thoracentesis in the diagnosis of pleural effusions. It is particularly helpful in the setting of suspected pleural tuberculosis and malignant pleural effusions. It has no role in the evaluation of transudates.

Indications

In order to understand the indications for needle biopsy of the pleura one must first be aware of its limitations. The procedure is blinded, in so far as the clinician is unable to view the fragment of pleura to be biopsied and frequently the biopsies obtained are quite small, or consist of intercostal muscle (pleural tissue yields approximate 70–85% in most studies) [34–38]. Naturally, yields are heavily dependent on the operator's experience. In one study of over 200 biopsies, an experienced lung team was unable to obtain pleural tissue only 9% of the time compared with a 27% failure rate among other teams [37]. In that study, 30% of biopsies were reported as diagnostic.

Another drawback inherent to needle biopsy of the pleura is that only the parietal pleura can be biopsied with this technique. This means that disease limited to the visceral pleura will be missed altogether, no matter how experienced the practitioner. In addition, biopsies may not be representative as they are limited to a narrow area around a single puncture site. Because pleural disease often skips entire sections of the pleural membrane or may involve predominantly the visceral pleura, closed pleural biopsies become a hit-or-miss procedure. While false positive results are rare, not exceeding 1% of cases, false negative results are unfortunately quite common [35].

There is wide discrepancy as to when closed pleural biopsy is indicated, but most clinicians will agree that it is worth attempting if and when thoracentesis has failed to yield a diagnosis in the case of an exudative pleural effusion, particularly if tuberculosis or malignancy is suspected. In my view, it should be incorporated into a stepwise approach to exudative pleural disease in which thoracentesis comes first, followed by repeat thoracentesis and closed pleural biopsy and finally thoracoscopy. Thoracoscopy has obvious advantages, but it is more expensive, time-consuming and requires more manpower.

Adding needle biopsy to thoracentesis; what can be gained by it?

Closed pleural biopsy is undoubtedly more time consuming than thoracentesis and requires additional expertise. But, what can one expect to gain from this extra effort in the diagnosis of pleural disease? The answer is: just enough to make it worthwhile. The two studies should be thought of as complementary. For example, pleural fluid analysis demonstrating a low Lactate Dehydrogenase (LDH) may be predictive of negative results with pleural biopsy [39]. Overall, the increase in diagnostic yield for malignant pleural disease when needle biopsy is compared to cytologic analysis of pleural fluid alone has been reported as 7% [38]. That is, a biopsy may be positive when fluid cytology is negative. The opposite may also be true, although this is of no clinical consequence as most physicians who perform needle biopsy send pleural fluid for analysis as well. Needle biopsy is far superior to thoracentesis alone in the diagnosis of pleural tuberculosis [40]. Overall, the negative predictive value for the combination of pleural fluid cytology and closed pleural biopsy has been reported as 56% when both of these are non-diagnostic of tuberculous or malignant pleural disease [41]. In other words, the combined procedure's diagnostic sensitivity for malignant disease approximates 79%, and for tuberculosis it is 71–88% [41,42].

How many biopsies should be obtained?

The question of how many biopsies should be obtained is important in so far as every additional pass with the needle poses an increased risk of

complications. Several authors have addressed this issue. It appears that the answer varies depending on the indication. Most authors would agree that four biopsies are sufficient for malignant disease. In one study the difference in sensitivity for malignant pleural effusion when one biopsy was performed was 54% compared with 89% with four biopsies [43]. In that study, one good quality biopsy was considered sufficient for the diagnosis of tuberculous pleurisy. Another study, however, found that the optimal number of biopsies needed to secure the diagnosis of tuberculosis was six or more. In that study, the sensitivity of needle biopsy for tuberculosis was 100% in those patients who underwent six or more biopsies or who had pleural tissue in two or more biopsy samples [44]. The overall sensitivity for pleural tuberculosis was 87%.

Contraindications

Contraindications to closed pleural biopsy are similar to those seen with thoracentesis and include the presence of an untreated coagulopathy or uncorrected systemic anticoagulation, clinically significant thrombocytopenia, and skin disease at the puncture site. In addition, pleural biopsy is contraindicated in patients with empyema due to the risk of abscess formation at the puncture site [45]. Because the risk of bleeding is greater than that encountered with thoracentesis, we avoid performing pleural biopsy in patients with platelet counts below 50 000/mm^3 and an INR greater than 1.5.

Technique

Generally, we follow the same procedure as for therapeutic thoracentesis, but instead of inserting the needle introducer with the telescoped catheter once proper anesthesia is obtained, and the presence of fluid confirmed, we insert the biopsy needle (see needle-specific techniques later). The use of imaging for needle biopsy is not as widespread as it is for thoracentesis, although some authors argue that this technique is under-utilized [46,47].

While it is helpful to be familiar with both the Cope and Abrams biopsy needles, most physicians continue to use the one they trained with for obvious reasons. Familiarity with a given needle increases yield and reduces complications [37]. There are, however, subtle differences between the Cope and Abrams needles which are worth mentioning. Because the Cope needle must be repeatedly withdrawn following each biopsy, the risk of pneumothorax with this needle is greater. Also, biopsies obtained with the Abrams needle tend to be slightly larger than those obtained with the Cope needle [48]. One study however, found no difference in diagnostic yield between the two [48]. Both needles are reusable once sterilized.

The Cope needle

The Cope needle (Figure 14.1) has four separate components: a stylet, two hollow trocars and an outer cannula. One of the trocars has a hook at its distal end while the other is blunt. The cannula containing the blunt trocar and stylet is inserted following anesthesia of the skin and pleural surface through a small skin incision (<1 cm). The blunt trocar and stylet are then replaced by the hooked biopsy trocar. During this exchange, an obvious connection is established between the outside air and the pleura through which air can enter the pleural space. We therefore ask the patient to hum audibly for as long as the exchange takes place, usually just a few seconds. This maneuver ensures an elevated pleural pressure which precludes ambient air from entering the pleural cavity and causing a pneumothorax. For the same reason, the proximal

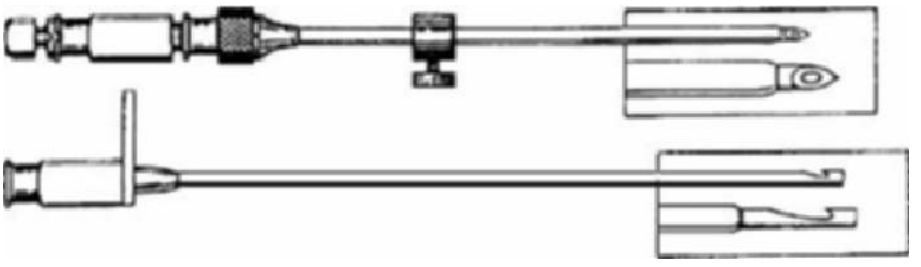

Figure 14.1 The Cope pleural biopsy needle.

hollow end of the biopsy trocar should be covered by the clinician's thumb at all times while obtaining the biopsy. Once the hooked trocar is in place, the needle is angled sharply over, never under, the rib, and aimed downward. Serial biopsies are obtained by retracting the trocar until a piece of parietal pleura is hooked, and gently advancing the outer cannula in a spiral motion over the trocar in order to dislodge the biopsy sample which drops into the hollow distal end of the trocar. The blunt trocar and stylet replace the hooked trocar in order to retrieve each biopsy from the latter. Generally, at least 4–6 biopsies are obtained. Some are processed by fixation and sent to the histology laboratory for staining while others can be sent under sterile conditions to the microbiology laboratory for culture.

The Abrams needle

The Abrams needle (Figure 14.2) is a closed system, i.e. serial biopsies do not mandate reinsertion of the needle. The Abrams needle has three components: an external trocar, an inner cannula and a stylet. An incision similar to that described for the Cope needle is also necessary. Careful preparation and anesthesia are equally important. The Abrams needle is inserted by applying a significant amount of force to the combined stylet, inner cannula and trocar which is blunt. The apparatus is made airtight by rotating the inner cannula such that the trocar's external notch is covered. One is aware of being inside the pleural space when a "pop" is heard, accompanied by a diminished resistance to the needle's advance. The stylet is then removed and replaced by a 60-cc syringe, followed by rotation of the cannula in order to provide access to the pleural fluid. The fluid can then be aspirated and sent for whatever diagnostic studies are felt necessary. Once enough fluid is obtained, the trocar's external notch must again be occluded by rotating the inner cannula thus rendering the apparatus airtight. This will allow replacement of the large syringe by a smaller less cumbersome 10-cc syringe.

Biopsies are obtained with the Abrams needle by gently withdrawing the needle, with the biopsy notch facing downward until it "catches." This means that the trocar has hooked a piece of tissue, which can then be confirmed as pleura by making sure that pleural fluid can still be aspirated into the syringe. At this point, the trocar must be held firmly while the cannula is rotated again in order to secure the biopsy. A slight resistance is expected as the hooked pleura is cut, coming to rest at the tip of the needle. The biopsy is then retrieved by either aspiration into the syringe or by removing the needle. Naturally, if the needle is withdrawn, air can enter the pleural space through the incision which must be covered with the clinician's finger in order to avoid this complication. All biopsies should be obtained below the horizon which is represented by an imaginary line drawn between the three o'clock and nine o'clock positions. This prevents damage to the neurovascular bundle associated with each rib. Once the requisite four–six biopsies are obtained, the needle is withdrawn and the site dressed appropriately. A chest radiograph is obtained following the procedure, regardless of the needle used, in order to rule out a pneumothorax.

Complications

The complications associated with closed pleural biopsy are similar to those seen with thoracentesis. The two main concerns are pneumothorax and hemothorax. The incidence of pneumothorax, however, does not appear to be greater with pleural biopsy when compared to thoracentesis. In fact, in one large Veterans Administration study

Figure 14.2 The Abrams pleural biopsy needle.

of 538 pneumothoraces at 13 medical centers, needle biopsy ranked fifth as one of the leading causes of iatrogenic pneumothorax, behind transthoracic needle biopsy, subclavian needle stick, thoracentesis and trans-bronchial lung biopsy [49]. Pneumothorax following closed pleural biopsy occurs in 3–15% of patients [50]. Hemothorax, though rare, has been reported [50], as has been seeding of the biopsy tract by tumor following pleural biopsy [51,52]. Rare complications such as perforation of the cecum, fracture of the biopsy needle, chest wall abscess, or intercostal arteriovenous fistula have also been reported [53–56].

Pleural fluid drainage; does chest tube size matter?

Traditionally, definitive pleural fluid drainage and sclerotherapy implied tube thoracostomy with a large bore chest tube. This procedure required hospitalization, often for a period of a week or more, and was not without substantial morbidity due to the pain associated with a large indwelling chest tube. Alternatives to this traditional approach have been sought in order to deal with malignant pleural effusions. Such effusions are accompanied by exceedingly high mortality rates and median survival often does not exceed 3–4 months [57,58]. A wide array of small-bore catheters have been designed in order to fulfill this need (Figure 14.3). The goal of therapy in these cases is to achieve rapid symptomatic relief in a cost-effective way, by better-tolerated, less invasive means, while preventing hospitalization in a patient who has just a few months to live.

One small randomized study compared a small-bore catheter with large-bore chest tube drainage and pleurodesis [59]. In that study, the small bore catheter was associated with less discomfort ($p < 0.05$), and was equally effective. Several retrospective studies have compared the efficacy of large bore chest tube drainage with small bore catheter drainage in the treatment of malignant pleural effusions [60,61]. Parulekar *et al.*, compared 58 cases of malignant pleural effusion treated with 12-F catheters with 44 cases in which large bore chest tubes were used [60]. All patients underwent pleurodesis in this retrospective study, and no difference in outcomes was found. Similarly,

Figure 14.3 The Pleurx© catheter. An outpatient option in the management of malignant pleural effusions.

Parker *et al.*, concluded that pleurodesis was as effective using small bore catheters when compared retrospectively with large bore chest tubes [61]. A series of other small studies have validated the use of various small bore catheters, some using sonographic guidance [62–64]. Small bore catheters have also been used to treat pneumothoraces and uncomplicated pleural effusions [65–67]. They have even been reported useful in the presence of trapped lung physiology, a frequent occurrence in malignant pleural effusions, and a concern invoked by some in favor of traditional chest tube drainage [68].

One particular advantage inherent to small-bore catheters is that they can be employed safely and effectively in the outpatient setting [69–71]. Another advantage in a cost conscious society, is cost savings. At least one study suggests that such small-bore chest tubes are more cost-effective than their traditional counterpart [66].

One large series published by Seaton *et al.*, proved these catheters not only to be effective but also quite safe. Of 47 patients studied, only 1 developed a transient fever associated with sclerotherapy [63]. A retrospective review from 1996 of 88 patients documented a high incidence of pneumothorax following small bore catheter placement [72]. Twenty-seven patients suffered this complication, although the pneumothorax resolved in the majority. Some

authors have advocated the use of imaging guidance because of this, although the clinical significance of such pneumothoraces is uncertain [73–75].

Unfortunately, controversy remains regarding the choice of procedure. This is most likely due to the fact that whatever literature exists on the subject reflects conclusions drawn from small, often retrospective case series. Randomized studies addressing this issue tend to be small and are otherwise uncommon. In addition, the wide variety of catheters available make it very difficult to generalize results from one particular study with regard to small bore catheter safety profiles, complication rates and cost.

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15 CHAPTER 15

Medical thoracoscopy

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Introduction

Thoracoscopy or pleuroscopy is a procedure in which the pleura is directly visually examined. It involves creating a pneumothorax and insertion of an endoscope through an incision in an intercostal space. The pleural space and its lining can be inspected and therapeutic interventions performed. The procedure can be done both under local and general anesthesia, is well tolerated and bears little side effects.

History

In 1908, Jacobaeus described an endoscopic investigation of the bladder, the bronchial tree and of the thoracic cavity. Especially the investigation of the thoracic cavity was "of no small value in making the differential diagnosis between tumors and primary pleurisy of other origin" [1]. In 1922, in the era of induced pneumothorax for the treatment of tuberculosis, Jacobaeus published his results on the thoracoscopic use of electrocautery to lyse adhesions between the lung and chest wall to allow a complete collapse of the lung.

Until the 1940s and 1950s thoracoscopy was used for diagnosis and therapeutic pneumonolysis for tuberculosis. With the discovery of effective tuberculostatic antibiotics the need for this intervention disappeared. During the 1960s glass fibers for medical purposes were introduced, providing a better and safer illumination technique for endoscopic applications. Supported by this technical improvement, thoracoscopy gained popularity in many European centers and was more often performed for the diagnosis and treatment of pleural effusions and pneumothorax. Both rigid and flexible optics were used [2,3]. Rigid scopes used for this purpose were easier to manipulate in the relatively wide pleural space and allowed larger biopsies. This explains why they are currently preferred for the inspection of the thoracic cavity [4–6].

A growing interest of North-American centers for medical thoracoscopy was noted around 1990. The interest was raised by the development of video-endoscopic surgical techniques, following the example of the first endoscopic cholecystectomy in 1989 [7]. General and thoracic surgeons developed the surgical thoracoscopy or video-assisted thoracic surgery (VATS), allowing for minimally invasive surgical procedures of the thorax, using for instance ENDO-Gia stapler and other techniques. Thoracoscopic endoscopic surgery with robotic surgical systems was first performed in 2001, when a thoracoscopic thymectomy with the da Vinci computer-enhanced surgical system was performed [8].

Medical versus surgical thoracoscopy

Medical and surgical thoracoscopy or VATS differ in methodology, use different equipment and are performed by different professionals, but still their boundaries are not clearly delineated. In general, surgical thoracoscopy is performed under general anesthesia and medical thoracoscopy under local anesthesia, sometimes in combination with sedation. Some authors however prefer general anesthesia for medical thoracoscopy, either for logistic reasons or the patient's comfort, and recently VATS was described as being performed under local anesthesia and sedation [9]. The number of ports of entrance into the thoracic cavity in medical

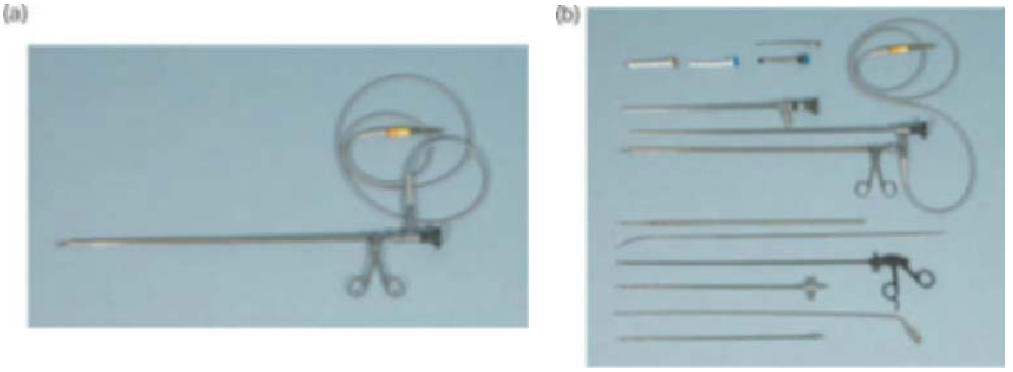

Figure 15.1 This figure shows some of the equipment used for medical thoracoscopy. (a) Shows a plastic trocar with a 7 mm (with obturator) and 5 mm diameter, and a metal 5-mm trocar and separate obturator, respectively; (b) shows a telescope with a 45° angle, and (c1) with a 0° angle. The latter can be inserted in the integrated biopsy forceps (c2), allowing biopsies to be taken under direct vision through only one working channel. The straight guide probe with centimeter indication (d1), the curved guide probe (d2), an insulated forcep for taking biopsies with simultaneous coagulation (e), suction tubes (f1 and 2) and puncture cannula (g) are examples of equipment that can be used via a second port of entry.

thoracoscopy is generally confined to one, whereas surgical thoracoscopy often involves three ports. Both procedures might use two ports of entry [10], and a single trocar technique for VATS also has been described [9].

The interventions performed by VATS are more extensive and include partial pleurectomy, staging lymph node biopsy, mediastinal mass biopsy and resection, diagnostic or therapeutic wedge resection, lobectomy or bullectomy using complex disposable retracting and dissecting instruments [11]. Medical thoracoscopy is mainly a diagnostic procedure confined to inspection of the pleural cavity and sampling of pleural biopsies using simple nondisposable equipment. But again more extensive resections, bullectomy, sympathectomy and pericardial fenestration have been performed by medical thoracoscopists.

Medical thoracoscopy is mainly performed by pulmonologists with special interest in interventional pulmonology [12]. Surgical thoracoscopy is performed by practitioners with a surgical background [13], who of course also may perform less extensive medical thoracoscopy. A related technique is called extended thoracoscopy, which allows for several large pleural biopsies to be taken in patients with thick adhesions that prevent normal thoracoscopy [14]. An alternative route to inspect the pleural cavity was described by Deslauriers, who performed the inspection of the pleural space by extension of a cervical mediastinoscopy to the medial part of either the left or right pleural cavity [15].

Equipment

An example of materials needed for thoracoscopy is given in Figure 15.1. Trocars with a diameter above 10 mm might be difficult to manipulate and are less convenient and more painful for the patient. For this reason 5- or 7-mm trocars are generally preferred, although a 7-mm trocar is too small to allow access to all integrated telescopes and forceps. Trocars can be obtained with different obturators, with blunt and with sharp points. Sharp obturators can more easily be introduced through the tissues of the thoracic wall, but are more prone to injure the lung after penetration of the parietal pleura. Blunt obturators are more likely to push the lung aside and are therefore preferred. Detachable rubber stoppers can make the cannula airtight, but in general a free airflow through the trocar does not interfere with the procedure. For electrocautery, trocars with insulated tips and interiors should be used.

After introduction in the thoracic cavity, telescopes with a 45°; angle can be rotated as a periscope, and by this simple action a complete

overview of the cavity can be obtained. Telescopes with views under different angles, like the 0° and 90° optics, can subsequently be used for a more closer inspection. The video camera and light cable should be correctly sterilized or covered by a sterile sheet. Various instruments are used through the working channel, like suction catheters, needles for cytologic puncture and forceps which allows the physician to take biopsies. These can be introduced via the same point of entry as the telescope, to take biopsies under direct vision, but can also be introduced via a second point of entry for the biopsy of lesions out of reach of the first port.

The set of equipment is completed with the sterile materials to cover the area of surgery, the local anesthetics, scalpel, sutures and sterile compresses. Anticondens solution might help to prevent condensation of fluid on the lens during the procedure. An endoscope warmer can be used for the same purpose. A talc atomizer and sterile, dry talc should be available for pleurodesis and a chest tube and underwater drainage set for drainage of the pneumothorax at the end of the procedure.

The endoscopy suite

The endoscopy room should allow the practitioner to perform a procedure under strict sterile conditions, with sufficient room for the procedure table, video equipment, the light source and monitoring equipment. It should allow for minimum interference between the thoracoscopist, nursing personnel and anesthesiologist [5–17]. It is recommended to perform the procedure under video observation to enhance the cooperation between these individuals [18]. The thoracoscopy table should be adjustable in height and if possible have moving surfaces to allow the patient to be positioned, and ideally the table should be suitable for fluoroscopy during the procedure. Other equipment includes an aspiration system that might contain several liters of pleural fluid, adjustable light, a stand for sterile display of the instruments and a display for X-rays. An electrocautery system might be present.

During the thoracoscopy the patient should be monitored carefully. Monitoring equipment for continuous registration of the pulse rate and saturation and regular measurement of the blood pressure are mandatory. Supplemental oxygen decreases the incidence and severity of hypoxemia in sedated patients, and should be available. A resuscitation kit and cardiac defibrillator should be on standby in case of an adverse outcome.

Induction of a pneumothorax

A prerequisite for performing a thoracoscopy is the induction of a pneumothorax. This can be performed at the start of the thoracoscopic procedure or beforehand. The latter option has the advantage that the position of the lung can be studied roentgenologically after inflation of air in the hemithorax, as is illustrated in Figure 15.2 [4,6,19]. Adhesions of the lung to the thoracic wall are visualized and pleural tumors might become visible, which can help with the choice of the proper point of entry. An X-thorax in the lateral decubitus position might provide additional information (Figure 15.3). The risk of bleeding complications after biopsy of the lung might be smaller too, since perfusion in the collapsed lung is likely to be diminished after 24 h.

In the presence of pleural fluid the pneumothorax can be induced by exchanging the pleural fluid by air. Portions of 50–200 mL pleural fluid can be removed and exchanged by air in a 1 : 1 ratio. Ambient air can be allowed to enter freely in the thoracic cavity or this can be done under fluoroscopic control [20]. The air should not be inflated under pressure to prevent injury of intrathoracic structures, or rupture of any adhesion [21]. Inflation of CO_2, like in laparoscopy, has not gained wide acceptance [20], although in this situation simultaneous monitoring of the expired carbon dioxide concentration allows for an additional tool to check the position of the needle in the pleural space [22]. Exchange of about 400–800 mL of air is sufficient to obtain a 30% pneumothorax [4] with a good view on the pattern of collapse of the lung on fluoroscopy.

Several methods are available to induce a pneumothorax in the absence of pleural fluid. Specific needles are designed to penetrate the parietal pleura without inducing damage to the lung [21]. The needle designed by Boutin has a pointed obturator, used to penetrate the thoracic wall under local anesthesia. Once the tip of the needle is localized at the parietal pleura, the pointed trocar

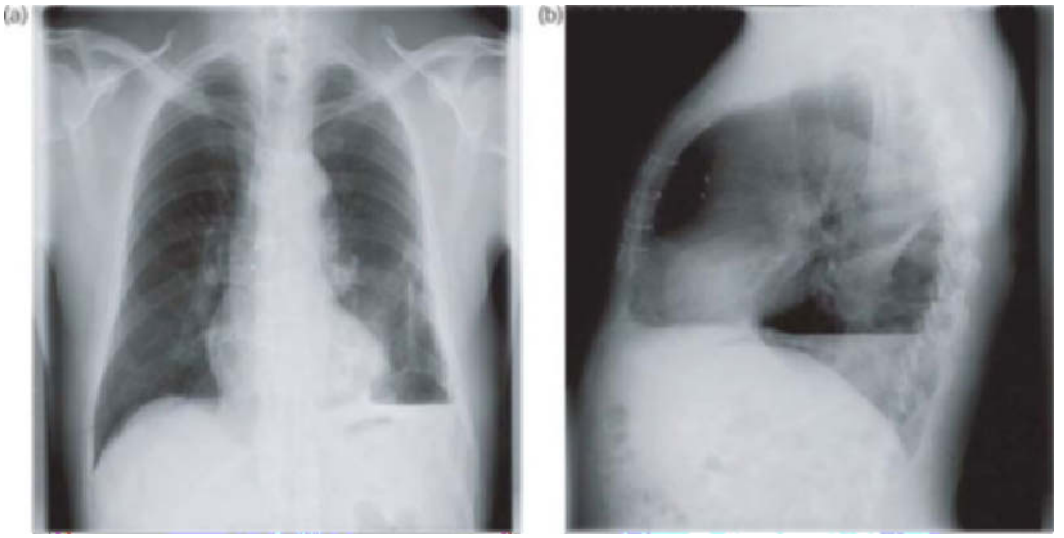

Figure 15.2 Roentgenological exam after induction of an artificial pneumothorax. The posteroanterior view reveals a small pneumothorax laterally (a) (arrow). The left upper lobe seems completely adhesive to the thoracic wall. The lateral view shows both the hydropneumothorax (b) (small arrow) posteriorly, and the adhesion (large arrow). The fifth intercostal space in the posterior axillary line was chosen as the point of entry for thoracoscopy.

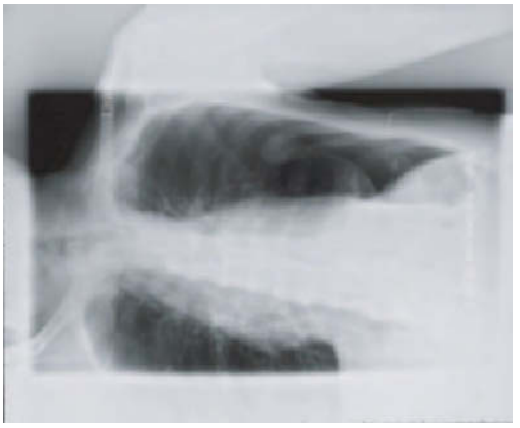

Figure 15.3 Roentgenological exam in the right lateral decubitus position after induction of an artificial pneumothorax at the left hemithorax. The arrows show a partial collapse of the left lung and the presence of an adhesion. The dotted line represents a pig-tail catheter used for induction of the pneumothorax.

is replaced with a blunt one, which then penetrates the pleura and allows air to flow into the pleural cavity, a feature that is often accompanied by a whistling noise. The needle can be connected to a manometer or a "pneumothorax apparatus" to monitor the fluctuations of the intrathoracic pressure during inspiration and expiration. Normally negative pressures of -8 to -2 cm of H_2O are recorded, oscillating parallel to the breathing excursions. Monitoring the pressure in the pleural space minimizes the chance of raising the intrathoracic pressure too high during this process. It is recommended to maintain pressure below $+5$ cm of H_2O [7,21]. Intrathoracic pressure below -10 cm of H_2O are an indication for a trapped lung. Low amplitude oscillations around the 0 point indicate that the tip of the trocar is either still in the thoracic wall or has pierced the lung accidentally.

Preprocedure evaluation

Before each thoracoscopy a patient should have a complete history and physical examination. Pleural and pulmonary pathology can be visualized by chest radiography and/or a Computed tomography (CT) scan. A bilateral decubitus film can help to establish the presence of pleural fluid and to localize adhesions after induction of a pneumothorax.

Depending on the indication, the anesthesia during the procedure and the comorbidity of the patient additional tests can be performed. Differences in preprocedure testing between different institutions are remarkable [2,4,5,16,23]. The

tests recommended by the American Society of Anesthesiologists depend on the physical status of the patient, the severity and type of the underlying disease, the comorbidity and medication of the patient [24]. In patients with a good physical status, who are 60 years of age or less no additional testing is required. However, most patients, who are candidates for thoracoscopy, are likely to have pulmonary symptoms, which may require evaluation of the respiratory status by blood gas analysis or pulmonary function tests. Depending on the comorbidity and the use of steroids, diuretics or other medication additional blood work including a hemoglobin, potassium, creatinine and glucose and an EKG can be added to the screening [24].

Thoracoscopy, like other invasive procedures performed through surgically scrubbed skin, is not likely to produce significant bacteremia associated with an increased risk for endocarditis and the prophylactic use of antibiotics is not recommended [25]. When the pleural space is infected it is advisable to administer antimicrobial prophylaxis, especially in individuals at risk for endocarditis [25].

Informed consent should be obtained whenever required.

Anesthesia

Medical thoracoscopy can be performed under local [26–28], regional and general [11] anesthesia depending on the possibilities and experience of the institution [12,28].

Proper local anesthesia induces a complete loss of senses of the intercostal structures. The intercostal nerve derives from the ventral branch of the thoracic spine nerve, and runs laterally at the inferior border of the ribs, initially between the pleura and the posterior intercostal fascia, but soon between the *M. intercostalis internus* and *intimus*. Skin branches are given off in the midaxillary line and at the anterior part of the thorax. The description of a four step anesthesia nicely draws attention to the sensitive structures of the thoracic wall, the epidermis, the aponeurosis of the thoracic muscles, the intercostal muscles and the parietal pleura [9], but usually local anesthesia is performed in one step with for instance lidocaine 0.5–2% [3,29]. Epinephrine may be added to the anesthetic but this has the theoretical disadvantage of inducing a vasoconstriction of the intercostal artery and since this is an endartery, perfusion defects might occur. Once pleural fluid, suspected of or with proven malignancy, has been aspirated in the syringe with lidocaine, use of this fluid for further subcutaneous injection might add to the chance for subcutaneous metastases.

A conscious patient, despite adequate local anesthesia, might still perceive considerable discomfort, lying in a less comfortable position for a period of time, being aware of the manipulation of the trocar and feeling pain when the parietal pleura is manipulated. Several authors recommend systemical sedatives, such as midazolam or droperidol [30,31], or propofol [9], in order to allow patients to tolerate the thoracoscopy while maintaining adequate cardiorespiratory function and the ability to respond purposely to verbal and/or tactile stimulation [24,32]. This level of anesthesia used to be referred to as "conscious sedation," but might more accurately be defined by the term "sedation and analgesia" [24].

A caveat concering the use of combinations of sedatives and narcotics should be kept in mind. The potentiating effect of morphines and benzodiazepines increase the likelihood of ventilatory depression and hypoxemia and may lead to respiratory and cardiac arrest especially in the elderly and in patients in a poor general condition [32]. These drugs should be appropriately reduced in dose when used in combination. An IV cannula should be in place to allow specific antagonists of opioids (e.g. naloxone) and benzodiazepines (e.g. flumazenil) to be injected in case of complications.

Sedated patients should have the pulse rate and saturation and blood pressure monitored carefully and continuously [24]. Electrocardiographic recording should strongly be considered in patients with hypertension, significant cardiovascular disease or dysrhythmias [24]. If available another individual other than the person performing the procedure should monitor the patient's status recording the ventilatory and hemodynamic status, the level of consciousness and amount of medication administered [33]. In some clinics a laryngeal mask is applied to safeguard the airways of patients, to prevent aspiration or upper airway block.

Medical thoracoscopy under sedation and analgesia can very well be performed as an outpatient procedure [34], provided that the recovery care has been of an adequate standard and the patients are observed until they are no longer at risk for cardiac and respiratory depression [24].

Medical thoracoscopy can also be performed under general anesthesia [2]. Double lumen intubation allows the lung to collapse more extensively, which provides a better view for the thoracoscopist, while the respiration is guarded by an anesthesiologist, but it does add to the complexity of the procedure and subjects patients to the risk of prolonged respiratory insufficiency after awakening. General anesthesia might be chosen in case of uncommon indications to allow rapid conversion to thoracotomy in case of a complication [35].

Technique

Entrypoint

The procedure is performed with the patient in the lateral decubitus position with the healthy lung down. By raising the arm over the head, where it rests in a sling, and arching the vertebral column upward by adjusting the procedure table, the intercostal space is widened and easily located by palpation. After positioning the lateral area of the chest is prepared and draped as for thoracotomy. The choice of the point of entry depends on the indication for that specific procedure and the presence of pleuropulmonary adhesions, as were visualized after the induction of the pneumothorax.

For orientation on the thoracic cage some landmarks are of help. The angulus sterni, or the angle formed by the corpus and manubrium of the sternum, indicates the level of the second intercostal space, which also can be felt in the midaxillary line at the top of the axillary hollow in nonobese people. This allows for identification of the ribs and intercostal spaces. The area 1–2 cm lateral of the sternum should not be used for introduction of the trocar, as the internal mammary vessels run there immediately behind the ribs.

An anterolateral approach via the fifth or sixth intercostal space in the midaxillary line is commonly used. One enters at the level where the fissura major and minor meet and allows inspection of all lobes of the lung. In case of a pneumothorax the thoracoscopy focuses on the apex of the lung and a higher point of entry, in the fourth or third intercostal space, might be chosen. A diagnostic thoracoscopy in a patient suspected of metastatic disease of the pleura should focus on the lower half of the hemithorax, where most of the metastases (84%) are found [28,36]. Almost all early metastatic lesions in this series of 203 patients with confirmed pleural carcinomatosis were found in the costodiaphragmic sinus, on the diaphragmatic and lower parietal and visceral pleura.

Once an artificial pneumothorax is present or if a large amount of pleural fluid allows direct insertion of the trocar, the latter can be introduced via a small stab incision and blunt dissection of the intercostal space. Incidentally, a large bore chest tube (32–36 F) has been used to allow introduction of a flexible bronchoscope to inspect the pleural cavity [3]. The trocar should be advanced carefully, corkscrew-wise to prevent injury to the lung or diaphragm. After removing the obturator, residual fluid can be drained and the thoracic cavity inspected.

An alternative method to gain access to the thoracic cavity and obtain biopsies when normal thoracoscopy is not possible due to thick pleuropulmonary adhesions uses an extended incision of 3–4 cm [14]. After blunt dissection of the intercostal space a cavity between the parietal and visceral pleura can be created digitally. The small cavity can be inspected and allows for sampling of biopsies under direct vision of the thoracoscope.

Chest tube drainage

At the end of every procedure chest tube drainage is required to remove the residual air from the thoracic cavity and to ensure that there is no airleak or bleeding. Rapid expansion of the lung is usually confirmed by a chest roentgenogram, allowing the tube to be removed within 2–4 h. Some centers tend to remove the drain more rapidly after uncomplicated procedures, when chest sounds have become normal again [34]. Most patients may then be discharged that evening or the following morning [7,37]. After talc nebulization the lung should be brought back against the chest wall as soon as possible, which might require a large bore chest tube (28–36 F). Removal of the tube should be considered when the production of pleural fluid is less than 100–200 mL per 24 h. The average

drainage time after talc pleurodesis is about 5 days [37]. Systemic drainage after biopsy of the visceral pleura and lung averages 3.5–5.3 days [10,38]. The time to adequately drain the hemithorax was significantly longer following lung biopsy in interstitial lung disease patients with a decreased total lung capacity [38].

Contraindications

Contraindications for medical thoracoscopy are either related to the procedure itself or to its anesthesia.

It is an absolute requirement that the pleural space be accessible for a thoracoscope. The minimal space required for insertion of a scope is about 1 cm, and the smallest cavity needed for creation of an artificial pneumothorax is at least 6–10 cm by 10 cm. Thick adhesions are considered to be a contraindication for thoracoscopy [29]. Furthermore, adhesions will limit the possibility to take adequate biopsies, accounting for false negative results [28].

Other procedure-related absolute contraindications involve honeycombing of the lung, since this is associated with vulnerable visceral pleura and a high risk of bronchopleural fistula. Suspected arteriovenous aneurysms, hydatic cysts, pulmonary hypertension and highly vascularized pulmonary lesions are also contraindications for medical thoracoscopy because of the high risk of potentially lethal complications. Refractory cough is associated with a high risk of subcutaneous emphysema, and the procedure might therefore be postponed in a severely coughing patient.

Conscious sedation is less suitable for procedures that last longer than 90 min. This form of anesthesia is contraindicated in patients who are not able or willing to cooperate, or who have extreme fear or stress-related disease, such as hypertension, recent myocardial infarction, angina pectoris, asthma or epilepsy, since the stress might trigger an exacerbation of these conditions [24,33]. Likewise, induction of an artificial pneumothorax in distressed patients can be complicated and result in unwanted puncture of structures such as the spleen [26].

Although respiratory insufficiency is a risk factor for prolonged respiratory support after general anesthesia, it is not considered a contraindication for medical thoracoscopy. In these patients the procedure is preferentially performed under local anesthesia [29]. Oxygen desaturation was noted in less than 2% in a review of 2500 patients who had their thoracoscopy under local anaesthesia [39]. A severe respiratory insufficiency with a pO_2 below 50 mmHg when breathing ambient air is an absolute contraindication [4]. Likewise, a low FEV_1 below 1 L/s is no absolute contraindication for medical thoracoscopy, especially in case the poor pulmonary function is due to the presence of pleural fluid. Exchange of the pleural fluid by air does not deteriorate the pulmonary function and is not likely to interfere with the thoracoscopy. Sixteen patients with a moderately decreased diffusion capacity (mean DCO\VA 48%) tolerated the induction of a pneumothorax without remarkable side effects [21].

A bleeding tendency, either involving a thrombopathy, coagulation disorders or vascular pathology, should be corrected before the intervention. And finally a well-known fact – advanced age is no contraindication for medical thoracoscopy.

Indications

The indications for medical thoracoscopy are listed in Table 15.1. Both diagnostic and therapeutic indications will be discussed.

Pleural effusion

Pleural effusion is a common symptom that accompanies numerous diseases and is by far the most frequent indication for medical thoracoscopy [7,29]. Pleural effusions are classified into transudates and exudates by criteria of Light based on the pleural fluid-to-serum protein ratio and the Lactate dehydrogenase (LDH) level of the pleural fluid, and the pleural fluid-to-serum LDH ratio [41]. Recently, these data were prospectively validated by Joseph *et al.*, who found that the absolute level of LDH in pleural fluid was the most accurate marker for diagnostic separation of exudate and transudate [42].

The most common cause for a transudate is cardiac failure, which accounts for more than 50% of all pleural effusions. Other causes for a pleural transudate are nephrotic syndrome and liver cirrhosis. The pleural surface generally is not involved in the primary pathological process [41]. Thoracoscopy is therefore not the primary diagnostic tool in transudates, although it should be considered

Table 15.1 Indications for medical thoracoscopy.

Diagnostic		
Pleura	Pleural effusions	Benign
		Mesothelioma
		Metastatic malignancies
	Pleural thickening	Benign (plaques)
		Primary pleural tumors
		Metastatic malignancies
	Pneumothorax	Primary
		Secondary
Lung	Diffuse lung pathology	
	Peripherally located lesion	
Mediastinum	Mass	
Therapeutic		
Pleurodesis	Malignant effusion	
	Recurrent benign effusions	
	Pneumothorax	
Debridement	Empyema	
	Hemothorax	
Other	Pleural foreign bodies [35,40]	

in recurrent transudates since pleural malignancies may present as such.

An exudate results from pathological processes involving the pleura, and investigations focusing on the pleura are therefore required. Medical thoracoscopy is a useful tool to establish the etiology of a pleural effusion, especially in case a thoracentesis is not diagnosed. The aspect of the fluid might point to the diagnosis in case of a hemothorax, an empyema or a chylothorax, but additional clinico-chemical workup, cultures and cytological examination are required to confirm the diagnosis.

A medical thoracoscopy should be taken into consideration when less invasive procedures such as thoracentesis, needle biopsy of the pleura or bronchoscopy are not or not likely to be diagnostic. The first step in the analysis of a pleural effusion generally is a thoracentesis with a diagnostic yield of cytologic examination of approximately 50% (Figure 15.4) [43]. The yield increases with

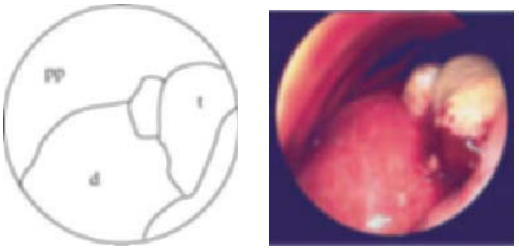

Figure 15.4 Thoracoscopic image of a man, who developed right-sided pleural fluid after metastasectomy of liver metastases from a colon cancer. Two thoracentesis revealed a greenish, biliary exudate. Cytologic examination of the fuid revealed no malignancy. Thoracoscopy showed metastases of an adenocarcinoma (t) that had invaded through the diaphragm (d). The parietal pleura (pp) appears slightly inflammated.

advanced disease in case of a malignancy and on repeat aspirations, which are positive in the second and third thoracentesis in about 65 and 70%, respectively [43].

The overall diagnostic accuracy of needle biopsy of the pleura moves around 60% [16,36]. In a consecutive series of 1000 patients with a chronic pleural effusion, a diagnosis was obtained in 785 patients by one or more cytologic and needle biopsies [4]. In patients with a diagnosis of malignant pleurisy only 53% had metastatic disease on the costal pleura, which might explain the relatively poor accuracy of blind needle biopsy in this patient group [36,44]. In turn, thoracoscopy provides the diagnosis in more than 90% (93–94%) of the patients with pleural disease of unknown origin [2,4,16,28–30,45]. Older series report a lower diagnostic rate, probably due to less advanced equipment [4,46]. The sensitivity of medical thoracoscopy was higher than that of cytology and blind pleural biopsy combined [16]. Even partial inspection of the pleura through extension of a cervical mediastinoscopy revealed the diagnosis in 78% of a selected patient population with bronchial carcinoma and in 92 of 102 patients with a benign pulmonary disease [15]. False-negative findings are mainly due to incomplete inspection of the pleural cavity due to multiple adhesions.

Malignant pleural effusions

The most common malignancies that tend to metastasize to the pleura are lung and breast cancer, accounting for about two-thirds of the malignant

pleural effusions [47]. The thoracoscopic appearance of the pleura does not differentiate between the different primary tumors, although metastases from a malignant melanoma may have a characteristic pigmented appearance. The most common aspects are pleural nodules or masses (37%), less frequently pleural thickening (26%) and a combination of the previous (21%), a lymphangitis or nonspecific redness is also seen [4].

In non-small cell lung cancer the presence of pleural fluid is usually an ominous sign. Involvement of the pleura by malignant cells renders the tumor non-resectable, but otherwise an effusion resulting from consolidation distal to an obstruction does not [48]. The guidelines of the British Thoracic Society recommend thoracoscopy in case two thoracenteses fail to show malignant cells in patients with an ipsilateral non-small cell lung cancer [49]. A negative thoracoscopy practically excludes the presence of a pleural malignancy [50]. In that case, the pleural fluid should not be taken into account as staging factor [51]. So far, no false positive result has been described.

A different strategy is direct thoracoscopy without preceding thoracenteses [28]. This approach revealed a malignant effusion in 78% of the lung cancer patients presenting with a pleural effusion. Talc poudrage was performed during the same procedure when frozen section examination of the pleural biopsies revealed no tumor cells [28]. Although this strategy seems quite straightforward, one should keep in mind the fact that in this population a single thoracentesis is diagnostic in 50% of the patients.

Pleural mesothelioma

In experienced centers, cytologic examination of pleural fluid might be quite accurate for the diagnosis of malignant mesothelioma, but many institutions prefer a diagnosis based on histological evidence. Compared to Abrams' biopsies, which is diagnostic in about 20% of cases, medical thoracoscopy has the advantage of being more sensitive. Thoracoscopy revealed the diagnosis of malignant mesothelioma in 98% of 188 patients, in a center where routinely 10–20 biopsies were taken in each individual patient [31]. This equals the high diagnostic rate of a thoracotomy, while being less invasive.

The aspect of the pleura in malignant mesothelioma can be quite diverse, from a nonspecific inflammatory or lymphangitic appearance to small nodules and from diffuse thickening to a pachypleuritis with large nodules and masses [31]. The pleura in early mesothelioma might be thickened, red, congestive with loss of transparency [31] or like sand granulations [52] or like a fibrotic pleurisy. It is recommended that biopsies are obtained from both abnormal and normal looking pleura from the parietal, diaphragmatic and visceral pleural surface for several reasons. Figure 15.5 illustrates that normal looking pleura might be infiltrated with malignant cells and on the other hand abnormal looking pleura might microscopically contain only aspecific inflammatory changes. The sarcomatous subtype of mesothelioma is characterized by ample stromal tissue, and larger and more tissue samples are needed to confirm the histological diagnosis of malignant mesothelioma [53]. A limited number of biopsies taken in this situation might lead to false-negative results. And additionally, differentiation between malignant mesothelioma and mesothelial hyperplasia can be difficult in small biopsies that do not show infiltration of normal tissue by the tumor.

Staging of malignant pleural mesothelioma

Local intrathoracic spread characterizes the growth pattern of malignant pleural mesothelioma, explaining most of the clinical symptoms that are observed in mesothelioma patients, such as thoracic pain, shrinking of the hemithorax, subcutaneous nodules and dysphagia. Roentgenologic estimation of local tumor spread is inaccurate, especially in early stages of the disease. Boutin published a series of carefully staged patients, describing significant survival differences between patients with different tumor involvement of the pleura [37]. In very early stages the tumor is confined to the ipsilateral or diaphragmatic pleura. In a later stage scattered areas of tumor studding are seen on the visceral pleura. Compared to patients with tumor confined to the parietal pleura with a mean survival of 32 months, patients with tumor involvement of the visceral pleura only had a mean survival of 7 months. This observation was incorporated in the TNM staging system proposed by the International

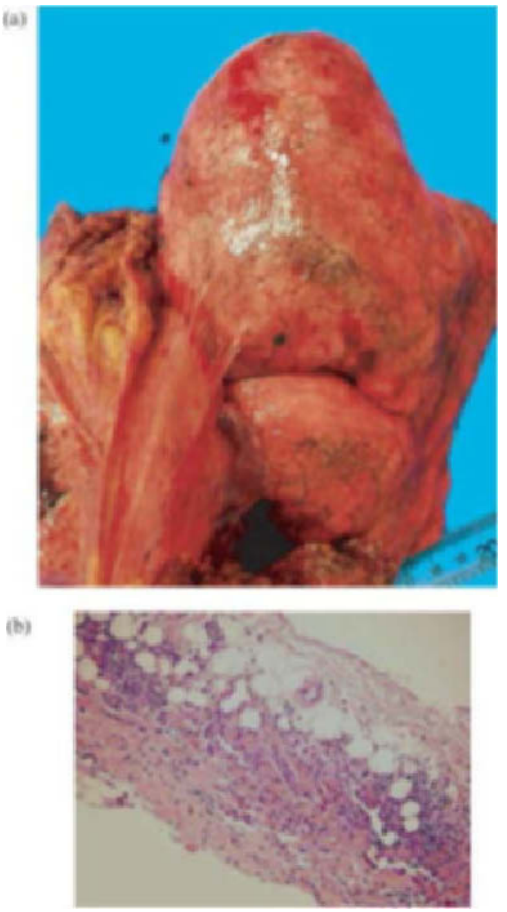

Figure 15.5 Figure (a) shows the lateral view of a left lung that has been removed by extrapleural pneumonectomy from a patient with an epithelial malignant mesothelioma of the left hemithorax. Macroscopically, the parietal pleura appeared normally both at thoracoscopy and during thoracotomy (a). In contrast, a diffuse infiltration of the pleura by tumor is shown by microscopic examination (b). The macroscopically abnormal lower lobe was only scarcely infiltrated with tumor cells, but consisted of fibrous tissue and inflammatory cells, probably as a response to a talc pleurodesis, that had been performed earlier (not shown).

Mesothelioma Interest Group that differentiates between tumors limited to the ipsilateral parietal pleura including mediastinal and diaphragmatic pleura (stage T1a), and tumors with additional scattered foci on the visceral pleura (stage T1b) [54] Stage T2 tumors are thoracoscopically characterized by confluent tumor on the visceral pleura, which often begins to fuse with the parietal pleura [54]. Other features of T2 tumors, involvement of the diaphragmic muscle and extension into the pulmonary parenchyma, cannot be evaluated by thoracoscopy.

Diffuse lung disease

Medical thoracoscopy is also utilized to obtain biopsies from the lung parenchyma. With a 5-mm double-spoon insulated coagulating forceps biopsies can be taken, while coagulating the cut surface of the lung to prevent a major airleak. A medium setting of 100 W is usually correct to prevent airleak without carbonizing the biopsy [5]. To avoid damage to the large fissural and mediastinal veins biopsies should not be taken from the interlobar fissure. The advantage over biopsies taken transbronchially is that the biopsies are usually larger and more likely to be diagnostic.

Nevertheless, medical thoracoscopy is not widely used in the diagnosis of diffuse lung disease. Some centers have gained considerable experience, with a diagnostic yield of thoracoscopic lung biopsies ranging from 90 to 100% [34]. Biopsies of 3 and 5 mm are sufficient for the diagnosis of e.g. allergic alveolitis, sarcoidosis, eosinophilic pneumonia and hemosiderosis [26,38,55]. In 57 of 63 patients (90%) with interstitial lung disease thoracoscopic lung biopsy was diagnostic, being not conclusive in patients with Wegener's disease, a case of tuberculosis and of multiple microemboli [26]. Macroscopically, the surface of the lung of patients with a interstitial lung disease showed areas with small irregularities [26]. In another study, in 10 of 24 patients with interstitial lung disease the pleura had a nodular, cobblestone appearance with thickened septa and blebs, the appearance of the lungs in the other patients being normal [38]. Sampling biopsies from visceral pleura with both a normal and abnormal appearance minimizes the chance to obtain just non-diagnostic biopsies with end stage fibrosis.

Interstitial, diffuse lung diseases are also frequently encountered in immunocompromised patients and in patients with connective tissue disease. Thoracoscopic lung biopsy in immunocompromised patients was diagnostic in 27 of 28 procedures, revealing e.g. *Pneumocystis carinii* and cytomegalovirus pneumonitis and interstitial fibrosis following irradiation or as a result of graft-versus-host disease [26]. The visceral pleura

in *P. carinii* infections shows white–yellow nodules dispersed throughout the lung surface [56]. These might be seen in association with large reddish nodules or multiple small apical bullae.

Apart from the interstitial abnormalities, patients with connective tissue disease frequently have associated pleural irregularities, which adds to the arguments for the use of thoracoscopy in these diseases. These lesions, although commonly observed at postmortem examinations or thoracotomy, rarely form a clinical problem, except in rheumatoid arthritis and systemic lupus erythematodes (SLE) [57]. Pleural involvement in rheumatoid arthritis may mimic bacterial pneumonia and empyema, but may also present as an asymptomatic chest radiographic finding. At thoracoscopy the visceral pleura shows various degrees of nonspecific inflammation, whereas the parietal pleura has a characteristic "gritty" appearance, with numerous small granules of about 0.5 mm in diameter. SLE patients with pleural effusions invariably have symptoms of dyspnea, cough and fever at the time of discovery of the effusion. The antinuclear antibody titer in the pleural fluid is supposed to be a sensitive test for SLE pleurisy, especially in titers above 1 : 320. However, malignant pleurisy might also have high antinuclear antibody titers.

Tuberculosis

At its introduction, medical thoracoscopy was almost exclusively used for the diagnosis and treatment of tuberculous pleurisy. Currently, only a small part of the thoracoscopies are performed to confirm the diagnosis of a tuberculous process. The diagnosis of pleural tuberculosis rests with the demonstration of *Mycobacterium tuberculosis* in the culture of pleural fluid or biopsy. The culture yield for pleural biopsy is 90–97%, which is considerably higher than that for pleural fluid (23–67% yield) [10,44,46,58,59]. Although other diseases have been reported to cause granulomas in the pleura, also histopathologic demonstration of the granulomas is generally accepted as diagnostic for tuberculosis [7,58]. Thoracoscopic findings in tuberculosis are mainly aspecific inflammatory changes of the pleura, but occasionally miliary white–yellow granulomas are seen [46]. Biopsy under direct thoracoscopic vision may be of value when blind pleural biopsy is not possible or fails to confirm the diagnosis.

Pneumothorax

Spontaneous pneumothorax is a relatively common disease in young adults, with an estimated incidence of 6/100 000 per year [60]. Its cause is mostly attributed to rupture of subpleural bullae or blebs, which are present in about 50% of the patients presenting with a pneumothorax [61]. The incidence of bullae and blebs does not differ between patients with a first or recurrent pneumothorax, but more blebs are present in the elderly and smoking patients, and are frequently found together with pleural adhesions [61].

Vanderschueren proposed a classification of four types in pneumothorax based on the thoracoscopic findings [62]. In type I the lung appears normal, in type II adhesions are present, in type III and IV bullae and/or blebs are present that are smaller or greater than 2 cm in diameter, respectively. The first three types might be managed thoracoscopically, while type IV might preferentially be treated by surgical intervention [63]. According to the consensus of the American College of Chest Physicians, the role of thoracoscopy in the management of primary spontaneous pneumothorax is limited to patients with a persistent airleak or for prevention of a recurrent pneumothorax [64]. The recurrence rate of a spontaneous pneumothorax that has been treated by rest or drainage is 22–28% [63,65]. Randomized trials comparing thoracoscopy with other treatment modalities are nonexistent. In the treatment of uncomplicated primary pneumothorax, tube drainage is the preferred treatment option. Thoracoscopic bullectomy of apical bullae and parietal abrasion of the upper half of the hemothorax either with or without video assistance was the preferred intervention for preventing pneumothorax recurrence [64]. Stappler bullectomy is generally not performed by medical thoracoscopy. Thorough pleural abrasion is difficult to perform and might require a third point of entry into the thorax to reach the whole cupula. This implies that surgical rather than medical thoracoscopy is the preferred therapy of choice [64,65]. Talc poudrage through the thoracoscopic cannula is an acceptable alternative, resulting in

recurrence rates of 2–10%, which is in the range of the recurrence rate after surgical abrasion (2%) [63,66]. Also in patients who are at high risk for a recurrence such as immunocompromized patients with a *P. carinii* pneumonitis or cystic fibrosis talc poudrage might be effective, although prolonged drainage and ineffective pleurodesis occur more often [56,66].

Mediastinal processes

The presence of mediastinal lymph node metastases has a major impact on the prognosis of lung cancer patients and greatly influences the choice of therapy. Paratracheal, subcarinal lymph nodes and nodes in the aortic pulmonary window generally are staged by mediastinoscopy. The presence of lymph node metastases in the para-oesophageal region or in the pulmonary ligament are more difficult to detect. The guideline of the British Thoracic Society on the selection of patients with lung cancer for surgery mentions thoracoscopy as a technique to obtain biopsies from lymph nodes from stations 8 and 9, although its value still has to be demonstrated for this purpose [48]. Recently the positron emission tomography (PET) scan has extended the view of the pulmonologist in the mediastinum [67], and endo-oesophageal and endotracheal ultrasound guided punctions are successfully introduced to obtain cytological evidence from enlarged lymph nodes [68,69]. Currently, these techniques are to be preferred above thoracoscopy for mediastinal staging of non-small cell lung cancer.

Therapeutic indications

Pleurodesis

Thoracoscopic talc insufflation is an effective and safe method of pleurodesis in patients with a malignant effusion. In comparison with other treatment options, such as a therapeutic thoracentesis, chemical pleurodesis via a chest tube or major surgical procedures, talc poudrage under thoracoscopic guidance permits an effective pleurodesis when a good view of the pleural cavity can be obtained, which allows an even distribution of the talc over the pleural surface [47].

The recurrence rate in a retrospective series of 327 evaluable patients was less than 10% after 1 month, with more than 80% of the patients showing a lifelong pleural symphysis [12]. Similar results were obtained in a prospective study, showing successful pleurodesis by talc insufflation in 95% of cases, with 91% of the patients still available for follow-up after 3 months [30]. The drain was removed after about 5 days, when the production of pleural fluid was less than 100 mL per 24 h, which resulted in residual pleural fluid between 100 and 500 mL in 4.3% of the patients.

Pleurodesis by insufflation of talc was also effective in the treatment of lymphoma-related chylothorax. Insufflation of 4–8 g of talc prevented the recurrence of the chylothorax in all 26 patients, again with a mean duration of chest tube placement of 4 days [27]. Alternatively, sterilized talc can easily and effectively be administered as a slurry at the bedside via a chest tube [70].

Another thoracoscopic method for pleurodesis is scarification of the pleura by Nd:YAG laser. This was successfully applied in the treatment of pleuritis carcinomatosa originating from prostate cancer [71].

In malignant pleural effusions secondary to breast cancer or lymphomas the recommended treatment is systemic chemotherapeutic and/or hormonal therapy. If symptoms are not relieved by this approach local treatment and pleurodesis must be considered [47].

Hemothorax

Hemothorax is a common manifestation of penetrating and nonpenetrating trauma, but is also noted after cardiac and pulmonary surgery, as a complication of a thoracic malignancy and might occur spontaneously. Blood coagulates rapidly in the pleural space, but the clot may be defibrinated probably as a result of physical agitation by cardiac and pulmonary movements. Drainage of a hemothorax is indicated to prevent the development of late complications such as empyema or fibrothorax. Because of the presence of blood clots and loculation of the effusion chest tube drainage might not result in effective evacuation of the effusion. Thoracoscopy allows to remove larger blood clots and to break down remaining loculations. Successful resolution of the hemothorax was accomplished by VATS in 23 patients with a

complicated hemothorax that did not resolve by chest tube drainage [72]. Also early intervention of hemothorax by VATS resulted in appreciable clinical improvement in all 12 patients with only minimal morbidity [73]. In selected cases medical thoracoscopy under general anesthesia seemed as effective as VATS in patients with a hemothorax due to chest trauma [74]. It allowed adequate exploration of the diaphragm and drainage of the pleural space and proved particularly advantageous when there were dense pleural adhesions, thick pleural fluid and/or an inability to collapse the lung.

Parapneumonic effusions and empyema

Parapneumonic effusions develop in up to 60% of patients hospitalized with bacterial pneumonia [75,76]. Most parapneumonic effusions resolve without therapy directed toward the effusion. Some effusions however do not resolve without tube thoracostomy. These are called complicated parapneumonic effusions which comprise empyemas, but also effusions with negative cultures. Empyema is defined as pus in the pleural space, and it remains a serious problem despite the widespread use of antibiotics in the treatment of pulmonary infections. Empyema usually is secondary to a pneumonia, but can also result from trauma and tuberculosis and less commonly from pulmonary gangrene, oesophageal perforation, tuberculosis and forgotten foreign bodies [40,57].

Apart from antimicrobiotic therapy, treatment strategies for complicated parapneumonic effusions include direct surgery, thoracoscopy, tube thoracostomy with or without fibrinolytics, or no drainage. These treatment modalities were compared by the American College of Chest Physicians, which concluded that surgery, surgical thoracoscopy (VATS) and thoracostomy with fibrinolytic therapy were equally effective, and were associated with the lowest mortality and need for secondary interventions [77]. The algorithm for managing patients with parapneumonic effusions proposed by Light advises first to treat a complicated parapneumonic effusion by tube thoracostomy and intrapleural fibrinolytic therapy [78]. By lysing the pleural adhesions that separate pleural loculae, fibrinolytics like streptokinase can help to drain all compartments with pus. In case no change for the better is obtained, open drainage or decortication is indicated [78]. However, a review of the randomized controlled trials on intrapleural fibrinolytic therapy in the treatment of parapneumonic effusion and empyema revealed insufficient evidence to support its routine use [79]. More studies are underway.

Medical thoracoscopy is not routinely performed in patients with parapneumonic effusions and empyema [75,76]. Thoracoscopic drainage and adhesiolysis by VATS was successful in 63 out of 73 patients with multiloculated empyema, in whom pleural drainage had failed to evacuate the empyema adequately [72]. Especially in chronic empyema, conversion to thoracotomy was required. Surgical thoracoscopic interventions seem to be most successful when carried out early in the disease [80]. Medical thoracoscopy can be equally as effective as was illustrated in a report on the successful evacuation of empyema by medical thoracoscopy in 6 out of 7 cases [30]. In one patient it was evident during the procedure that thoracoscopy alone would not be satisfactory and that surgical decortication was indicated. Even in critically ill patients, some of who required preoperative ventilatory support, empyema was drained effectively by rigid thoracoscopic debridement [81,82]. After the procedure, the hemithorax can continuously be irrigated with a normal saline solution helping to clear the hemithorax [81,83]. Apart from therapeutic clearance of the empyema, thoracoscopy might reveal useful information of the underlying illness, and discover foreign bodies or esophageal fistulas [82].

Taken together, the small series on the treatment of empyema thoracis by medical thoracoscopists mention complete relief in about 60% of the patients. The other patients require a thoracotomy and decortication for effective clearance of the pleural space, although a small part of these (septic) patients might be unable to tolerate this major surgery [40].

Complications

Table 15.2 gives a summary of the most frequent complications of medical thoracoscopy. It illustrates nicely that medical thoracoscopy is a safe procedure, well tolerated, with a low morbidity rate [2]. In comparison with Abrams' needle

Table 15.2 Complications of medical thoracoscopy.

Complication	*Number of complications*	*Total number of thoracoscopies*	*%*	*References*	*Remarks*
Hemorrhagic					
hemorrhage, major	4	1150	0.3	4, 7, 9, 71	
hemorrhage, minor	1	24	4.2	38	
hemoptysis	1	75	1.3	10	
Infectious					
fever	67	660	10.2	7, 9, 10, 12, 30, 38	Almost all related to talc insufflation
empyema	6	1208	0.5	4, 29	
wound infection	4	173	2.3	6, 26, 30	
delayed wound healing	1	360	0.3	12	
Airleak					
prolonged airleak/ drainage time	53	654	8.1	7, 10, 12, 26, 38	Most frequently after lung biopsy
recurrent pneumothorax	15	242	6.2	10, 26, 30, 38	Most frequently after lung biopsy
subcutaneous emphysema	42	1660	2.5	4, 7, 39	
Mediastinal emphysema					
Air embolism	1	556	1.7	39	
Systemic					
Collapse	3	1556	0.2	4, 39	
asymptomatic cardiac ischaemia	1	1000	0.1	4	
Arrhythmias	3	149	2.0	7, 9	
medication-induced confusion	1	24	4.2	27	
severe shortness of breath	41	632	6.5	27, 30, 39	
ARDS	1	24	4.2	27	
Technical					
adhesions preventing adequate thoracoscopy	7	556	1.3	39	
Local					
tumor infiltration in the scar	11	1238	0.9	4, 6, 29	
Total	263	2566*	10.2		

* This figure gives the sum of all thoracoscopies described in each individual reference.

biopsies, the complication are comparable [44]. Also the mortality rate is low. Two deaths were noted in a review of 2298 cases by Viskum and Enk [39]. However, thoracoscopy-related death is rarely defined in papers on this subject. Mortality within 30 days after the procedure occurs more often than the figures presented earlier suggest, especially in severely ill patients, for instance with empyema, and is in this situation attributed to the disease rather than to the thoracoscopy [12,40,56,72].

The first complication may already occur at the start of the procedure. Creation of intercostal access in 2 out of 76 patients with empyema caused a diaphragmic injury [72]. In a distressed patient the induction of an artificial pneumothorax was complicated by unwanted puncture of the spleen [26]. Precautions should be taken to prevent injury of

the diaphragm both in patients with a change in anatomic proportion and also in those who are anxious.

During the procedure, the most common side effect is pain, either induced by manipulation of the trocar between the ribs, by biopsy or coagulation of the parietal pleura or being in an unusual and uncomfortable position for a period of time. Cough and dyspnea are not regularly noted as side effects [55]. Probably they are considered too insignificant to be mentioned [39]. Hypoxemia is observed in less than 2% of the patients [39]. It might be due to central hypoventilation caused by the morphinomimetics or sedatives, or by the pain, minimizing the respiratory movement of the chest wall, or by a lesser capacity of the lung when collapsed. The hypoxemia recovers almost invariably on the administration of oxygen.

Subcutaneous emphysema can become gross and a fatality has been described due to this cause. Massive subcutaneous emphysema might require a tube thoracostomy to recover [7]. Subcutaneous emphysema can develop especially when no drain is placed into the thorax after the procedure. Prolonged airleak and persisting pneumothorax is mentioned, but could be managed conservatively in all cases [39]. At risk were patients with a pleural malignancy, who had undergone lung biopsies and who had a low compliance of the lung (under 120 mL/cmH_2O) [7,26,38].

Empyema was the most frequent complication seen by Canto *et al.* [29] occurring in 6 out of 208 patients. Three patients had large amounts of fluid and three persistent air leaks, all requiring prolonged tube drainage. In two other studies comprising 444 patients, 6 developed empyema, which were all treated without difficulty [39], but lower incidences of around 0.1% also have been reported [4].

Bleeding may occur during the procedure, especially when biopsies are being taken [15]. Also pleural scarification using a Nd:YAG laser is mentioned as a cause of lesion of an intercostal artery [71]. Small bleeding points may be controlled by placing the metallic suction tip on the vessel and cauterizing the area. Major bleeding requiring transfusion was reported six times in a review on 356 patients, and occurred only once in a large series of 1000 patients [4,39]. The intercostal vessels (and nerve) lay in the groove at the caudal margin of the ribs. Therefore a biopsy is preferentially taken at the surface of a rib and not in the intercostal space, although arteriosclerotic vessels might meander over the surface of a rib. Another predilection place for bleeding are adhesions between the lung and thoracic wall. These might become vascularized, and cause a bleeding when damaged. For the same reason the interlobar fissures should be avoided during biopsy.

A late complication of thoracoscopy, especially in malignant mesothelioma but also in metastatic pleural effusions, is subcutaneous tumor ingrowth along the tract of the thoracoscopy trocar. Infiltration of tumor in the thoracoscopic scar occurred in 0.5–4% of the patients with a malignant pleurisy [4,29]. Radiotherapy (3×7 Gy) of the scar after healing of the wound prevented tumor seeding in 20 patients, whereas tumor seeding did occur in 9 out of 20 patients who had not been irradiated prophylactically [84]. Patients from this institution have since then been systematically irradiated, and this complication has no longer been seen [34]. Other, and prospective data showing that preventive radiotherapy is superior to selective, palliative radiotherapy of patients who develop symptomatic subcutaneous metastases are not available.

Air embolism is a rare, but serious complication that has been reported when the procedure was performed with the patient in a sitting position [46,85]. Ventricular tachycardia and vascular collapse complicated the induction of an artificial pneumothorax in one patient [7].

Medical thoracoscopy is a procedure with a history that lasts almost a century at this point of time. The shift in the epidemiology of tuberculosis and lung cancer in the twentieth century and of malignant pleural mesothelioma during the previous 20 years have changed the indications for medical thoracoscopy. Technical improvements have been introduced, but the principles of the procedure have not changed. The technique is simple. It has the major advantage that it can be performed under local anesthesia with a low complication rate even in patients with major comorbidity. The diagnostic efficacy is high, and thoracoscopy is therefore referred to as the "golden standard" for several disorders. Because of its excellent features medical thoracoscopy will continue to move forward as a

major diagnostic and therapeutic tool for pleural diseases in the twenty-first century.

Acknowledgments

The author would like to thank Prof. J.P. van Meerbeeck for helpful and stimulating discussions during the preparation of the manuscript, and Ms. R. de Wijk-van der Zalm for her skillful technical assistance.

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16 CHAPTER 16

Photodynamic therapy in the pleural space

Paul Baas, MD, PHD, FCCP

Introduction

For intra-thoracic application, photodynamic therapy (PDT) has primarily been tested in malignant pleural mesothelioma (MPM) as additional treatment during surgical resection. The results, so far, have not lead to an improvement of survival and have showed quite some toxicity. A number of reasons can be attributed to this lack of success. Aspects of the photosensitizers used, the dosimetry system and toxicities encountered will be discussed. Furthermore a new application of photosensitizers in the diagnosis of pleural malignancies is presented. Initial results of the use of photodynamic diagnosis (PDD) in MPM will be discussed. Improvements in the application of PDT, the dosimetry and implementation of active chemotherapeutic regimens are required to achieve better results.

For many years it has been a challenge to find a successful treatment for tumors confined to the thoracic cavity. Surgical treatment alone has proven effective for benign disease only while the ability to achieve complete tumor eradication of malignant tumors has remained the most important reason for failure. For some tumors that are confined to the hemithorax like mesothelioma and cases of primary pleural adeno-carcinoma, adjuvant therapies are indicated after extensive surgical resection. Well known adjuvant modalities are irradiation, given per-or postoperative, adjuvant chemotherapy or chemotherapy given perioperative under hyperthermic conditions [1–4]. Results achieved by these approaches are contradictory, therefore novel, more promising methods were introduced. One of these less well-established forms of experimental treatment is PDT.

The basic principles of PDT are as follow: after the administration of a photosensitizer the patient stays in subdued light till the scheduled operation takes place. After surgical resection of the visible tumor (laser) light of a wavelength that coincides with one of the absorption peaks of the sensitizer is given to the tumor-bed till a predefined amount of energy is delivered. After completion of the treatment, the patient is returned to the ICU for recovery from the procedure.

For an optimal result of the intrathoracic PDT the following criteria have to be met. The diagnosis must be confirmed and extensive stages of the disease must be excluded. The calculated postoperative cardiopulmonary function must be sufficient to allow an extrapleural pneumonectomy (EPP). For the PDT procedure it is important to consider the type of photosensitizer, dosimetry aspects and the type and setting of the laser.

Photodynamic diagnosis

One of the challenges in malignant pleural disease is to delineate the involved sites of the malignancy for optimal staging. Lesions on the parietal surface are sometimes difficult to identify due to reactive fibrin tissue reactions and therefore malignancy cannot easily be ruled out. In case of early MPM, the diagnosis may be missed due to sampling error. A method to identify pathologic areas would therefore be of great value.

Photodynamic diagnosis has been reported to have this ability but for intra-thoracic tumors no reports on this application have been published so far. The PDD can be divided in autofluorescence or photosensitizer mediated fluorescence [5,6]. In both methods, abnormal fluorescence images are obtained when light of a specific wavelength is changed and reflected by tumor tissue. The reflected light is passed through a long pass filter and is compared to the normal reflection spectrum.

In autofluorescence the increased reflection of red light is considered to be related to changes in vascularization, increases in the cell layer thickness, changes in tumor cell metabolism and increases in the concentration of chromophores [7]. There are a number of companies that offer standard systems that can be used for early diagnosis of Barrett's esophagus, cervical and lung cancer. For the application in the thoracic cavity adjustments have to be made by the local physics department.

The drug most often used in photosensitizers mediated PDD is 5-amino levulinic acid (5-ALA). This naturally occurring precursor of hemoglobin is administered orally, locally or intravenously 3–5 h before the procedure. The drug is given in a relatively low dose (15–30 mg/kg) and is retained in both normal and malignant cells [8]. In normal cells 5-ALA is readily metabolized to Protoporphorin IX (PP-IX) and subsequently into Heam. In general, tumor cells lack the enzyme ferrochelatase that facilitates the metabolism of PP-IX to Heam. As a consequence, the PP-IX concentration in the tumor cell will be increased compared to the surrounding, normal cells. PP-IX fluoresces when activated by green light and will emit red light of a specific wavelength that can be visualized in real-time. This method appears to be useful in the early diagnosis of Barrett's esophagus, GI malignancies and possibly in early lung cancer [9,10]. PDD is now under investigation in specialized centers to determine its additional value compared to standard examination. For malignant mesothelioma an example is presented in Figure 16.1(a,b) where the different fluorescent images are shown for standard white light and 5-ALA PDD. In this patient with MPM, white light inspection during thoracoscopy identified tumor nodules that were highly fluorescent after the administration of 5-ALA. Tumor areas can better be distinguished from the surrounding tissue. Pathologic examination of these specimens confirmed the tumor in the lesions with intense reflections and connective tissue at the control sites [11]. Although the number of patients examined so far is too small to make a final statement, the use of 5-ALA PDD seems promising.

Intrathoracic photodynamic therapy

Selection of patients

Radical surgery in patients can sometimes be achieved in certain tumors (e.g. PNET, localized forms of MPM). In the great majority of patients with MPM, however, the growth pattern of the disease is diffuse and *en block* resection with truly negative histological margins is not feasible [12]. The disease often invades adjacent structures such as the thoracic facia, diaphragm, lung mediastinum or chest wall. Therefore one can only achieve a macroscopic removal of the disease, also known as debulking. This can be accomplished by "simple" pleurectomy or the EPP [13]. EPP with or without resection of the diaphragm and pericardium is associated with significant changes in the hemodynamic and pulmonary reserves of the patients. The risks of postoperative mortality and morbidity are considerable. For optimal staging and selection of patients a detailed work-up has to be performed. Adequate postoperative pulmonary and cardiac function is essential for these patients. Important issues to consider before surgery are: the appearance of shrinkage of the afflicted hemithorax, which implies that the surgical procedure will be very difficult; a performance score greater than or equal to 2 according to the ECOG; weight loss greater than 10%; thrombocytoses; the appearance of multiple diagnostic ports. Other prognostic factors are: non-epithelial histology, pain, gender, age and diagnostic delay [14,15].

Photosensitizers

For the treatment of large surfaces such as the thoracic or abdominal cavity, only two commercially available photosensitizers have been used. (i) Photofrin® (di-hematoporphyrin derivate) is a more purified form of a group of mono and polymers that can be derived from blood. It has

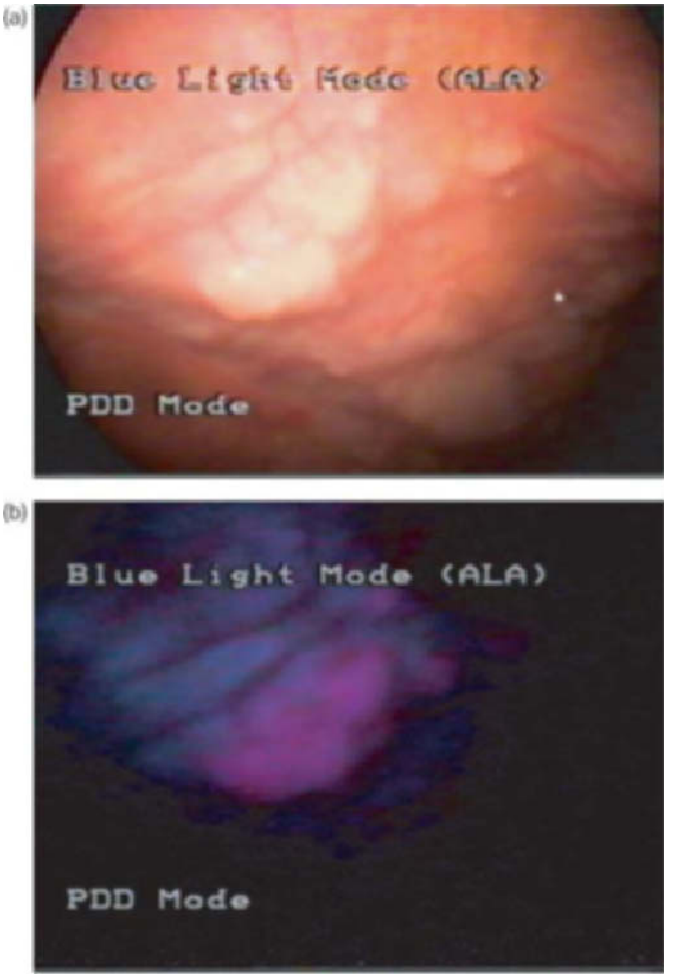

Figure 16.1 (a) Thoracoscopic view of mesothelioma located on the parietal pleura. The surrounding tissue is thickened and has signs of inflammation. (b) Same tumor as (a) but now with 5-ALA mediated fluorescence. The distinction between tumor (purple fluorescence) and surrounding tissue (bluish fluorescence) is more expressed.

major excitation wavelengths in the UV (200–450 nm) and the green (510 nm) and a small absorption peak in the red (630 nm) [16–20]. At 630 nm the light has only a limited tissue penetration and a relatively low singlet oxygen yield. Several investigators have used this drug after FDA approval [17–19]. (ii) Meta-Tetrahydroxyphenylchloride (Foscan®) is the second drug that has been tested in MPM. It has major absorption peaks in the UV (200–450 nm) and the green (520 nm) and a major peak in the red at 652 nm [20]. The penetration depth of light at this wavelength is strongly dependent on tissue properties but can reach depths of 1.0–1.5 cm. The singlet oxygen yield is approximately 30 times higher in the red light band than Photofrin®. Both drugs are administered intravenously and have different pharmacokinetic properties. Photofrin® is usually given in a dose of 2.0 mg/kg 2 days before the illumination to achieve a good tissue concentration. For Foscan® the dose is 0.1–0.15 mg/kg and the drug-light interval varies from 2–4 days. The drugs have some affinity for tumor cells itself, but more important, they are retained by the abnormal endothelial cells of the tumor vessels. This effect of vascular closure by PDT is considered to have a significant secondary effect on tumor cell eradication [21–23].

One of the most important side effects is skin photosensitivity due to retention of the drug in the skin. For standard dosages of Foscan® this is

generally less than 4 weeks, for Photofrin® less than 8 weeks. Other side effects of the sensitizer, such as allergy, have hardly been observed.

Laser equipment

For the treatment of a large tumor volume with PDT, high power light sources are required. In general the light used in PDT is derived from lasers to obtain a short band of light which coincides with one of the absorption peaks of the spectrum of the photosensitizer. Argon dye or Copper-Vapor lasers were initially used because of the ability to adjust the wavelength. In the 1990s it became clear which photosensitizers were most often used and therefore which wavelengths were required. Advances in technology resulted in the production of diode lasers at different wavelengths. The diode lasers have a fixed wavelength, are transportable, have power outputs up to 6 W (in the red light waveband) and do not require the use of high power supply or water cooling [24]. This facilitated the use of intra-operative PDT significantly. The technological advancements also resulted in a great number of laser fibers with different light applicators such as bulb ends, cylindrical diffusers and lens tips.

Dosimetry

One of the most important issues in the application of PDT is to find the optimal conditions for PDT-mediated tumor cell kill with minimal damage of normal tissue. However, some damage to the surrounding normal tissue is necessary to achieve maximal vascular shut down [25]. During this process cytokines and vaso-active compounds will be produced. The therapeutic window will therefore become smaller when larger areas are treated.

The light delivery system used in most reported studies is based on flat photodiode light detectors which measure only incident light fluence but not scattered and reflected light [26]. Such detectors clearly give an underestimation of the total fluence delivered to the tissue surface and therefore increase the total time of illumination. Initially the calculation of the total light dose was made by holding a photodiode in a section of the cavity that was illuminated by a lens-tipped fiber. In a sequential order all other parts of the cavity were illuminated by repositioning the photodiode and the lens-tipped fiber. This approach did not take into account the scattering and reflections of light and could therefore lead to an underestimation of the actual delivered light dose [27]. Other investigators have used flat photodiode detectors and a light scattering medium in the thoracic cavity [18,19]. The illumination probe was then positioned at multiple sites to achieve an optimal illumination on the sites where the photodetectors were placed. This method has the disadvantage that for tissues in regions between the photodetectors, the actual delivered light dose could not be calculated. The physics group of Rotterdam and thoracic oncology department in Amsterdam have developed an important improvement for the application of PDT in the thoracic cavity [28]. After EPP, four spherical miniature photodetectors are placed on strategic sites in the empty chest cavity. A transparent sterile bag is placed in the cavity and filled with warm saline to allow the tissue to stretch as much as possible (Figure 16.2a,b). After partial closure of the surgical wound a single spherical bulb fiber is placed in the center of the bag to allow an integral illumination of the entire cavity and enhance the reflection of light. In the majority of cases this could be achieved within 30 min of illumination. Failure to achieve an integral illumination was primarily due to insufficient relaxation of the diaphragm for which additional illumination was required (Figure 16.3a,b). The anatomy of the sinuses of the diaphragm does not easily allow additional illumination for which a wedge-shaped transparent cast was made. It included a centrally located cylindrical diffuser and photodetectors that were placed near the surface of the cast (Figure 16.4). These developments in dosimetry have given us more insight into the physics of the light treatment and reduced the chances of over or undertreatment [29].

Clinical studies

The first studies combining surgery and PDT were published in 1994 [18,19]. Both investigators used Photofrin® as photosensitiser. In the first study by Takita (Roswell Park Cancer institute) the surgical treatment was pleuropneumonectomy or pleurectomy. The median survival for the 23 patients entered was 15 months and for those with limited disease extension was 36 months. In the survival

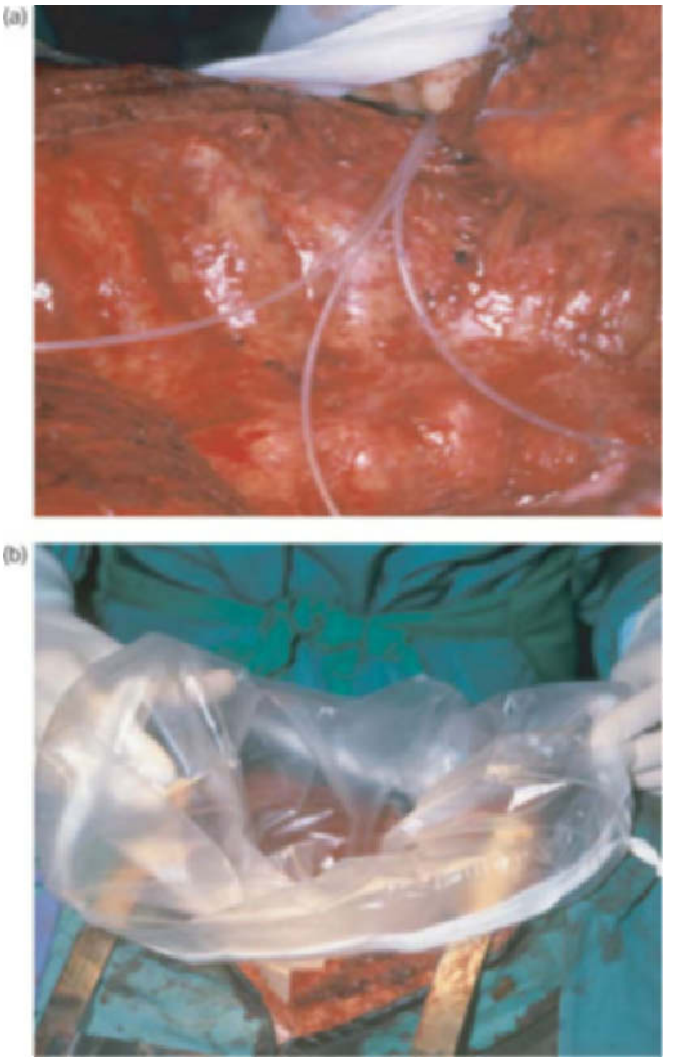

Figure 16.2 (a) View of the thoracic cavity after pleuropneumonectomy. Three of the four sterile tubes containing the isotropic detectors are placed on strategic sites in the cavity (apex, near the bronchial stump, the diaphragmal sinus). (b) After placement of the isotropic detectors the sterile plastic bag is filled with saline to stretch the diaphragm and reduce oozing of blood after the surgical procedure. The wound will be approximated and laser light will be administered by a bulb fiber which is placed in the center of the sterile bag.

analysis 3 patients who died of treatment related causes were excluded from the calculation. This group even reported on the 6-year survival [30]. Serious postoperative complications occurred in 12 patients: infections (6 pts), prolonged ventilator support (4 pts), cardiac arrhythmia (4 pts), bronchopleural fistula (3 pts), chylothorax (1 pt), hematothorax (1 pt), superior vena cava syndrome (1 pt) and rupture of the spleen (1 pt).

Pass (NCI, Bethesda) performed a Phase I study in 40 patients [19]. The choice of surgical resection depended on by the extent of the disease but was kept as limited as possible. The illumination procedure was performed with real-time dosimetry using flat photodiodes. The calculated median survival for all patients was 10 months, without perioperative mortality. Postoperative complications occurred in 15 patients: supraventricular arrhythmia (11 pts), congestive heart failure (2 pts), gastric ulcer and perforation (1 pt) and delayed healing of the thoracotomy wound (1 pt). Based on these results a Phase III study was initiated. After surgical resection patients were treated with or without intra-operative PDT. The treatment was followed by a combination of chemo and immunotherapy (Cisplatin and Tamoxifen) [31]. The PDT procedure was applied according to the Phase I protocol. In this study 63 patients were entered but no

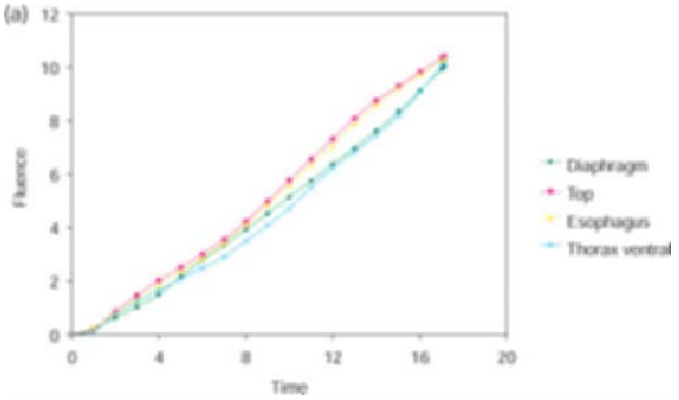

Figure 16.3 (a) Fluence J cm^{-2} versus exposure time in minutes. The light fluence is recorded by 4 isotropic detectors which are placed on strategic sites in the thoracic cavity. The increase of the fluence is synchronic for all sites. (b) As in (a) but now the light distribution is not equal over the isotropic detectors. The dorsal sinus and ventral part of the thorax do not receive enough light within the 10 min of illumination. Additional light is given for these sites using the wedge.

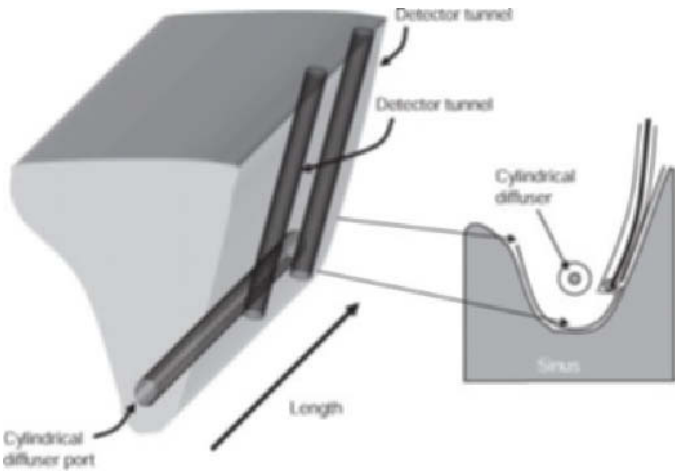

Figure 16.4 Wedge-shaped diffusing block made of transparent material. There is one port to fit the cylindrical diffuser and two side ports in which the isotropic detectors can be placed. (Figure adapted from van Veen *et al* [29] with permission).

difference between the two groups was found with respect to median disease-free survival (PDT 8.5, no PDT 7.7 months), survival (PDT 14.1, no PDT 14.4 months) or incidence of complications.

The first experience with mTHPC as a photosensitizer in thoracic malignancies was reported in 1991 by Ris, Switzerland [32]. In a later stage he reported his experience in eight patients with thoracic malignancies in 1996 [33]. The PDT was performed without real-time light dosimetry, so only an estimate of the delivered light doses could be made. Of the eight patients treated three

suffered from severe postoperative complications: colonic perforation (1 pt), bronchopleural fistula (1 pt) and aspiration pneumonia (1 pt). Several patients succumbed due to causes related to distant manifestations of MPM. Whether the PDT had accomplished a local complete control was not reported.

A pilot study on the use of mTHPC in patients with mesothelioma using real-time dosimetry measurements was published in 1995 [28]. The feasibility of this approach using the earlier mentioned isotropic detectors and expansion bag in the thoracic cavity after pleuropneumonectomy was confirmed and a subsequent Phase I/II study was carried out. In this study doses of Foscan® were escalated while the illumination times and surgical procedures were kept the same [34]. All patients had a pleuropneumonectomy and the drug light interval was 4 days for the majority of patients. The illumination was performed as shown in Figures 16.2 and 16.3 and lasted until a total fluence of 10 J cm^{-2} was achieved on all sites. In this study a total of 28 patients with a performance score of 0–1 (ECOG) were entered. In 2 of these patients a pleuropneumonectomy could not be performed due to extra-thoracic growth of the tumor. At the third dose level (0.15 mg/kg Foscan®) dose limiting toxicity was observed. In the other groups there was also considerable toxicity observed which was partly related to the extent of the surgical resection and partly due to the PDT. Especially patients with bulky tumors who presented with a retraction of the involved thoracic cavity had more postoperative complications. Reversible toxicity like excessive fluid accumulation in the thoracic cavity and atrial fibrillation were the most frequently observed. Rupture of the diaphragm (2 cases), myocardial infarction due to blood loss (1 patient) and cardiac tamponade were severe complications that required medical intervention. Three patients died in the postoperative period, of which 2 were in the highest drug level. The first patient had preexisting cardiovascular disease and a complicated resection of a large tumor. Hypotension due to blood loss resulted in a myocardial infarction that did not recover despite supportive measures. A post mortem examination (day 6 after treatment) revealed a large anterior myocardial infarction and generalized vascular disease. Histology samples of the treated chest wall revealed necrotic tumor nests without viable cells, indicating that the PDT had been effective. The second patient died 13 days after treatment. Two days before his death a bronchopleural fistula with bacterial infection was diagnosed by bronchoscopic examination. Unfortunately the patient refused further surgical intervention. The third patient died as a consequence of incorrect placement of the isotropic detectors in the thoracic cavity. It resulted in an overdose of light at the mediastinal structures, leading to an esophageal–pleural fistula. This complication was managed by placement of an omental flap and the construction of a Clagett thoracotomy. An unexpected bleeding in the cavity from multiple sites on day 12 was fatal. Late sequels of the combination treatment were also observed. Empyema presented as delayed toxicity in 4 patients 3–6 months after the procedure. Although local control could be achieved in 50% of the 26 patients the median survival time in this small group was only 10 months. The conclusion of the authors was that Foscan® mediated PDT cannot be recommended at this stage to be used without further improvements of the PDT technique and better patient selection.

Conclusions

Indications for the use of PDT in the thoracic cavity have not lead to results that allow its widespread use. As in all new therapies that are combined with other modalities it is more difficult to truly determine the attribution of the new modality to both the success of the combination and its side effects. Furthermore, the number of variables determining the effect of PDT (type of sensitizer, light dose, drug dose, drug light interval, methods of light measurement) requires support from a physicist, which restricts the number of clinics that can apply the treatment to date.

The studies reported so far have focused on the treatment of patients with malignant mesothelioma, a disease for which still no successful treatment is available. Although this allows researchers to perform Phase I and II investigations we must bear in mind that the final outcome of these studies with respect to survival is of limited value. The only Phase III study reported unfortunately showed no advantage for the use of PDT in combination with

surgery and immuno chemotherapy. Data available should be interpreted in the context of local control, safety and reliability of light application. Perhaps the impact of intrathoracic PDT in other malignancies such as pleuritic carcinomatosis or after resection of invading chest wall tumors will be more successful.

For PDD the use of low doses of sensitizing drugs like 5-ALA has to be further investigated. PDD could be useful to improve the diagnostic yield for tumors that are accompanied by great amounts of connecting tissue and to better localize the extent of the tumor. The initial results of 5-ALA mediated PDD are promising.

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17 CHAPTER 17

Intrapleural therapy: from BCG to therapeutic genes

Andrew R. Haas, MD, PHD *& Daniel H. Sterman,* MD

Introduction

Surgical resection for early stage non-small cell lung cancer has been the cornerstone of curative intent for patients with lung cancer for decades; however, surgical resection can be complicated by contamination of the pleural space resulting in postoperative empyema. In the early 1970s, [1–3] several groups reported improved survival in patients who developed a postoperative empyema compared to similarly matched postoperative patients without empyema. The prevailing theory held that the inflammatory environment of the empyema recruited lymphocytes to the pleural space to generate an antitumor immune response that could improve disease control and survival. While these reports were all retrospective reviews with many inherent limitations, and more contemporary analyses have questioned these results [4–6], the hypothesis was generated that the pleural space could be utilized as a reservoir for the treatment of advanced lung cancer, primary pleural tumors such as mesothelioma, metastatic pleural neoplasms and even nonmalignant systemic diseases.

Based on these early reports that postoperative empyema may improve lung cancer survival, several groups investigated the hypothesis that bacillus Calmette–Guerin (BCG) injection into the pleural space would generate a nonspecific immune response that could have similar antitumor effects as empyema, without the associated empyema complications. The earliest reported study of a small group of patients randomized to a single dose of postoperative intrapleural (IP) BCG versus saline instillation suggested a potential survival advantage in stage I disease [7]. Based upon these encouraging results, several larger randomized trials were undertaken. Unfortunately, none of these trials demonstrated a survival advantage with IP BCG compared to control [8,9]. In fact, these studies suggested that BCG treatment may actually enhance tumor growth rather than suppress it. Based on the results of these studies, further investigations into BCG as adjuvant therapy for lung cancer were not pursued; however, the pursuit of using the pleural space as a delivery mechanism to treat malignant mesothelioma (MM) or metastatic pleural malignancies had not ended.

Many investigators have continued to investigate the possibility of utilizing the pleural space as a means not only of treating MM or metastatic pleural neoplasms, but also of manufacturing proteins that are deficient in systemic genetic disease (e.g. alpha-1 antitrypsin [α1AT]). These investigations have been pursued in three primary pathways (or combination of these pathways): IP chemotherapy, IP immunotherapy and IP gene therapy. We will consider each of these three treatment modalities separately.

Intrapleural chemotherapy

Mesothelioma, thymomas and thymic carcinoma are tumors of the thoracic cavity that are notorious for locoregional spread of disease as opposed to distant metastases. Although surgical resection can be attempted, the presence of residual

microscopic disease is virtually guaranteed for MM and thymic carcinoma. Therefore, many groups have investigated whether local control of these malignancies can be achieved by instilling chemotherapeutic agents into the pleural space (IP) either alone or in combination with surgical debulking of the primary tumor. One such example was a recent study by Refaely *et al.*, published in 2001, in which the authors reported their experience with IP chemotherapy in 15 patients who had either thymic carcinoma ($n = 5$) or thymoma ($n = 10$). These patients all underwent surgical resection with intraoperative hyperthermic treatment with 150 mg/m^2 of cisplatin. One patient with thymic carcinoma was alive at 54 months and eight patients with thymoma were alive without evidence of recurrence at 9–70 months. While two patients developed significant bleeding, no other major toxicities were reported [10].

Given the extremely poor response rates to all therapies for MM, some groups have attempted to develop multimodality treatment approaches to improve the dismal prognosis of this disease. Pinto *et al.* treated 22 patients with MM with IP mitoxantrone in combination with intravenous methotrexate and mitomycin. They reported 1 complete response (CR), 6 partial responses (PR) and 7 with stable disease (SD). Although the overall median survival time for the entire group did not exceed historical median survival (13.5 months), the individuals with a response did have a median survival of 18 months compared to 8 months for nonresponders. Furthermore, there were significant reductions in dyspnea (68%) and pain (33%) following treatment [11].

Other groups have taken a more aggressive approach to the management of MM by utilizing extra-pleural pneumonectomy (EPP) followed by IP chemotherapy to control microscopic residual disease. Chang and Sugarbaker have recently reported their results of a Phase I clinical trial combining EPP with intraoperative cisplatin at a dose of 225 and 250 mg/m^2. These doses were higher than can be achieved by intravenous administration due to systemic toxicity; however, their study demonstrated these doses can be tolerated without significant toxicity when administered IP [12]. This group plans to pursue Phase II and III studies combining EPP with high-dose IP cisplatin.

Although MM and thymic tumors are relatively rare malignancies, metastatic pleural disease is much more common and is associated with significant morbidity due to dyspnea and pain and portends a poor prognosis. Consequently, many groups have investigated whether IP chemotherapy could be a modality to manage malignant pleural effusions (MPE), particularly those due to lung cancer given its high incidence of pleural dissemination.

In 1999, Tohda *et al.* treated 68 patients with MPE due to lung cancer with IP cisplatin (80 mg/m^2) and etoposide (80 mg/m^2). The overall response rate was 46.2%, the median survival time 32.3 weeks, the 1-year survival rate 28.7% and the 2-year survival rate 12.8% with minimal systemic toxicity [13]. A more frequent dosing regimen was pursued by Shoji *et al.* by the placement of an indwelling pleural catheter for the biweekly IP instillation of 5-flourouracil and cisplatin in 22 patients with MPE. They demonstrated essentially no systemic toxicity and a median survival period of 403 days with the longest survival period of 792 days [14]. This study suggested that repeated IP chemotherapy may be more advantageous than single dose IP therapy.

A more extensive combination therapy approach was investigated by Su *et al.* whereby 27 patients with lung cancer and MPE received sequential treatment with IP cisplatin followed by intravenous gemcitabine, thoracic irradiation and finally intravenous docetaxol. The overall response rate was 55% with 7% CR, 48% PR, 22% SD and 22% progressive disease (PD). Only 2 patients experienced recurrence of pleural effusion and 1-year survival was 63% [15]. To ascertain whether IP chemotherapy actually had an effect on malignant cells in the pleural space, Matsuzaki *et al.* resected the primary lesion in 11 consecutive patients with MPE and subsequently treated them with IP cisplatin (200 mg/m^2). They collected pleural fluid and malignant cells before and after treatment and stained them to determine the degree of apoptosis induced as a result of therapy. They demonstrated a dramatic increase in the number of apoptotic cells in patients treated with IP cisplatin versus patients who had surgical resection alone (25.2 versus 2.8%, respectively). In addition, while the median survival time for patients receiving the perfusion treatment was

20 months, the median survival time for the control group was 6 months [16]. Therefore, not only did IP chemotherapy appear to have a survival advantage, but also there was evidence that IP therapy could significantly increase apoptosis of malignant cells in the pleural space.

There are many limitations to these studies as they all are small case series using historical controls for survival and outcomes as opposed to well-controlled, randomized trials. Nonetheless, there does appear to be enough cumulative data to suggest that pursuing IP chemotherapy as an option for either MM, thymic tumors or MPE from metastatic pleural disease is warranted.

Intrapleural immunotherapy

The immune system is an extremely complex system with multiple levels of control, regulation and coordination that prevents autoimmunity, but allows for recognition and destruction of foreign, non-autologous antigens. For many years, the prevailing theory held that neoplasms averted an immunologic response because they were derived from normal tissue and thus they were not recognized by the immune system. With the advent of genomics and proteomics, it has become evident that tumor cells differ substantially in many ways from normal cells and that the immune system does recognize these aberrant tumor cells. Unfortunately, at multiple levels, the tumor and its microenvironment suppresses the ability of the immune system to have any substantial antitumor response to control disease. With this new understanding of the immunologic processes involved in cancer, many groups have investigated mechanisms to enhance the immunologic response against MM or metastatic pleural tumors.

Like many human malignancies, MM appears to be resistant to mechanisms of immune-mediated destruction. In "immunogenic" tumors, such as malignant melanoma, immunotherapy via exogenous cytokines, monoclonal antibodies and tumor vaccines has demonstrated some significant responses. Immunotherapy has been applied to MM, despite the observations that MM cells induce intratumoral downregulation of cellular, cytokine and humoral immune responses, which might significantly inhibit any approaches to augment the antitumor immune response [17]. In particular, high levels of TGF-β elaborated by mesothelioma cells and tumor-infiltrating macrophages cause downregulation of CD3 molecules on the cell membrane of tumor-infiltrating T-lymphocytes leading to a state of immunologic "tolerance" [18,19]. Mesothelioma cells express abundant class I major histocompatibility complex (MHC) molecules, but only small amounts of MHC class II molecules, and there is no demonstrable expression of the important co-stimulatory molecule B7-1. This results in minimal natural killer (NK) cell antitumor activity, poor presentation of tumor antigens to CD4 helper T-lymphocytes and inadequate stimulation of CD8 cytotoxic T-lymphocytes. In addition to the tumor's innate mechanisms of immune evasion, it has been demonstrated that patients with MM have impaired immune systems: abnormal humoral and cell-mediated immunity; abnormal cell-mediated antibody-dependent cellular toxicity; and defective macrophage and NK cell function [19–22]. High local levels of certain pro-inflammatory cytokines may, however, be able to overcome MM's innate immune resistance. This rationale has supported several human clinical trials demonstrating varying degrees of tumor regression with IP or systemic infusion of various cytokines, including interleukin-2 (IL-2) [23], interferon-α g(IFN-α) [24] and interferon-γ (IFN-γ) [25,26].

Results of a Phase I/II clinical trial entitled "Activity of IP Recombinant Gamma-Interferon in Malignant Mesothelioma" were published in 1991 [26]. The study protocol involved the administration of 40×10^6 U ($\sim$2000 mcg) of interferon via an implantable IP catheter twice a week for 8 weeks on an outpatient basis in 22 patients with MM. Toxicity was minimal with no dose limiting side effects. Tumor response was evaluated by chest Computed tomography (CT) scan and by thoracoscopy. CRs (with negative pleural biopsies) were seen in four of nine patients with Stage IA disease (tumor limited to the parietal and diaphragmatic pleurae). Of note, the patients who had CRs all had pleural nodules less than 5 mm in diameter. An additional Stage IA patient had a PR for a total response rate in this group of 56%. Only 1 of 10 patients with Stage II disease had a PR and there were no complete responders in this group.

Based upon the encouraging results in early-stage disease in this initial trial, a prospective, multi-institutional Phase II study of IP IFN-γ in MM patients was conducted using a similar protocol [25]. Eighty-nine patients with Stage I–III disease and both epithelial and mixed histologies were enrolled in the study. There were 8 histologically confirmed CRs and 9 PRs (>50% reduction in size of tumor). This corresponded to an overall response rate of 20% (similar to that of single-agent chemotherapy trials), but a response rate of 45% in patients with Stage I disease (tumor involving the pleural surfaces only). Patients with Stage IA disease had a response rate of 61.5% with a 2.5-year survival rate of 71%, remarkable for this fatal disease. Median survival among all Stage I patients was 28 months. The constellation of toxicities was similar to that seen in the preliminary trial, with the most serious complication being empyema in 7 of 89 patients, 6 of whom required removal of the pleural catheter. Fourteen patients required temporary interruption of therapy because of toxicity, with 12 patients necessitating treatment stoppage secondary to various complications, none of which were fatal or Grade 4.

In an adjunctive study, the pharmacokinetics of IP IFN-γ in pleural fluid and blood were measured in six patients [27]. Twenty-four hours after subcutaneous injection, the maximum level of IFN-γ observed in pleural fluid was 1.14 U/mL, whereas the maximal pleural fluid IFN-γ level seen 24 h after IP infusion was 10 891 U/mL. By 96 h after single IP injection, pleural IFN-γ levels decreased slowly to 173 U/mL. Corresponding serum levels of IFN-γ after IP injection were "low." This study clearly demonstrated that significantly higher levels of agents can be delivered to the pleural space by direct instillation as opposed to intravenous administration.

Administration of IL-2 in patients with MM, either alone or in combination with autologous lymphokine activated killer (LAK) cells, has been evaluated by several groups. Based upon *in vitro* data demonstrating LAK cell mediated lysis of cultured mesothelioma cells in the presence of IL-2, a small pilot Phase I trial was conducted in Australia in which patients received IP LAK cells and recombinant IL-2. Tumor responses were not reported and there was significant attendant toxicity, including several pleural space infections, non-cardiogenic pulmonary edema, liver enzyme elevations, flu-like illness and skin rash. One of five patients died as a result of encephalopathy and non-cardiogenic pulmonary edema [28].

Recent European Phase I–II clinical trials of IL-2 administered by continuous IP infusion via a subcutaneous pleural catheter revealed a 19% PR rate with significant dose-related toxicity, primarily the development of ipsilateral empyemas [29]. Of note were the high IP : systemic ratios of IL-2, approaching 1000 : 1 in the highest dose levels [23,29]. Researchers at the University of Turin (Italy) conducted a clinical trial involving combined systemic and IP IL-2. At interim analysis in 1997, 31 patients had been enrolled with a response rate of 22.5%, although 90% of patients demonstrated significant reductions in pleural effusion, presumably from an inflammatory pleurodesis. Toxicities were minimal, primarily fever, eosinophilia and mild cardiac and neurologic side effects [30]. A report describing infusion of activated macrophages into the pleural space followed by IFN-γ instillation several days later did not show any appreciable effect on tumor growth or survival in patients with MM [31].

Other investigators have focused their attention on the use of colony stimulating factors to initiate an antitumor immune response. Davidson's group at the University of Western Australia has conducted a Phase I clinical trial involving direct intratumoral injection of granulocyte–macrophage colony-stimulating factor (GM-CSF) with some local reduction in tumor mass associated with an intense intratumoral lymphocytic infiltrate in two patients [32]. This same group has demonstrated significant therapeutic effects with intraperitoneal (i.p.) delivery of cytokine genes for IFN-γ, IL-2 and antisense TGF-β in a murine model of mesothelioma [18,33].

Combinations of immunotherapy (cytokines) and chemotherapy have been evaluated in a series of Phase I and Phase II clinical trials in MM. These trials have as their rationale *in vitro* synergistic anti-proliferative effects on MM cell lines of cytokines such as IFN-α in combination with standard chemotherapeutic agents. In human trials, most investigators have focused on the use of the most-active single chemotherapeutic drugs such as doxorubicin, mitomycin and cisplatin in

combination with cytokines with proven antitumor activity (i.e. IFN-α). No significant difference in survival or relapse rates have been noticed in comparison to single modalities; however, further trials need to be evaluated [34–36].

Availability of IFN-γ for clinical use in Europe limited further study, but a pilot study of IP IFN-γ for MPE secondary to lung carcinoma was conducted in Japan [37]. Six patients with MPE underwent 1–3 weekly instillations of IFN-γ via a pleural catheter at doses of $1–12 \times 10^6$ U. Two of the six patients had complete clearance of malignant cells from their pleural fluid. An additional patient had a partial radiographic response after 2 IP instillations of 4×10^6 U of IFN-γ. No significant toxicities were noted. Pleural IFN-γ levels averaged approximately 5×10^6 pg./mL 24 h after IP injection; serum levels were in the range of 5×10^1 pg./mL. Interestingly, IFN-γ infusions did not, however, induce effective pleurodesis.

In a prospective, randomized trial, Sartori *et al.* compared IP bleomycin versus IFN-α2b in patients with recurrent, large MPE. While there was no significant difference in median survival (96 days for bleomycin versus 85 days for IFN-α2b), 30-day response was 84.3% in the bleomycin arm and 62.3% in IFN-α2b arm ($p = .002$), and median time to progression was 93 days in bleomycin group, and 59 days in the IFN-α2b group ($P < .001$) [38]. This study suggested that IP chemotherapy with bleomycin was superior to IP immunotherapy with IFN-α2b in control of MPE; however, there was no survival advantage, but a palliative advantage in terms of MPE control.

In addition to the various aforementioned specific immunotherapeutic agents, other investigators have attempted to stimulate a broad immune activation within the pleural space in combination with other treatment modalities to control pleural disease. These studies utilize inactivated bacterial superantigens from streptococcus (OK-432) or staphylococcus to stimulate a broad immune response in combination with other treatment modalities. Yamaguchi *et al.* combined OK-432 with IL-2 into the pleural space in 16 patients with documented MPE from colorectal cancer. There was a cytologic disappearance of cancer cells and decrease of effusion in 9 of 11 (82%) patients treated with OK-432 alone and in all 5 patients treated with OK-432 plus IL-2. Of particular interest, their immunologic analysis demonstrated that OK-432 plus IL-2 induced autologous tumor-reactive CD4+ Th1 killer lymphocytes which recognized tumor antigen presented with HLA class II [39]. In a Phase II study, Ikehara *et al.* treated 15 patients with MPE with IP OK-432 followed by standard systemic chemotherapy with cisplatin and gemcitabine. Of the 15 patients, 1 achieved PR, 13 had SD and 1 progressive disease with an overall response rate of 6.7%. The median survival time was 13.5 months and the 1-year survival rate was 60%. Compared to historical controls they report a better survival with this combined therapy compared to standard chemotherapy [40].

In a more recent study, Ren *et al.* instilled staphylococcal super antigen (SSAg) into the pleural space of patients with Stage IIIb lung cancer with poor performance status (ECOG PS greater than or equal to 2) [41]. Fourteen consecutive unselected patients received IP SSAg once or twice weekly until pleural effusions resolved. Eleven patients had a CR and 3 had a PR of their MPE. In 12 patients, the response endured for more than 90 days, with a median time to recurrence of 5 months (range, 3–23 months). Median survival of the 14 SSAg-treated cases and 13 consecutive talc-poudrage-treated patients with comparable pretreatment performance status was 7.9 months and 2.0 months, respectively ($p = 0.0023$). Nine of 14 patients treated with SSAg survived more than 6 months, 4 patients survived more than 9 months and 3 patients survived more than 350 days. One of the patients in the CR group has survived 36 months. None of the 13 talc-treated patients survived more than 6 months. These data seem to corroborate that nonspecific activation of the immune system can have significant effects not only on local control of MPE, but also potentially on survival.

Finally, a recent case report of a patient with refractory, large bilateral MPE due to non-Hodgkin's lymphoma (NHL) was reported. The patient had CD20+ NHL and bilateral MPE that were refractory to all standard therapies. Rituximab, an anti-CD20 monoclonal antibody that has revolutionized therapy for CD20+ lymphomas, was instilled into the pleural space via the chest tubes in increasing doses over 2 weeks. Within that period of

time, the pleural effusion resolved and the patient remained symptom-free 8 months following this therapy.

While many of these immunotherapy investigations indicate this form of therapy may be a feasible option for MM or recurrent MPEs, as stated earlier, they are limited by their lack of randomization and appropriate control groups. Nevertheless, with the minimal toxicities associated with these therapies, more effort must be made to pursue larger randomized controlled trials to ascertain if these therapies should become realistic additions to the armamentarium of treatment modalities for pleural neoplasms.

Intrapleural gene therapy

Approximately 15 years ago, advances in molecular genetics and gene transfer technology made the development of "gene therapy" (the modification of the genetic makeup of cells for therapeutic purposes) a possibility for medicine. Although the disorders originally proposed as targets for gene therapy were the inherited, recessive disorders in which transfer of a normal copy of a single defective gene could potentially alter the course of a disease, it soon became apparent that the range of target diseases could be extended to acquired disorders, such as inflammatory diseases and cancer. The concept of gene therapy now encompasses the treatment of any pathophysiologic state based upon the transfer of genetic material, including complementary DNA (cDNA), full-length genes, RNA or oligonucleotides. This definition also includes approaches where genetically altered cells are introduced into an animal or patient.

Gene therapy involving the pleural space offers a number of potential advantages. The pleural space has a large surface area lined by a thin layer of mesothelial cells, the ideal configuration for efficent gene transfer. Liquids or cell suspensions injected into the pleural space would disseminate rapidly and uniformly, potentially allowing a very large number of cells to be transduced. The patterns of fluid drainage from the pleural space through vascular and lymphatic channels would ensure rapid systemic uptake. In addition, access to the pleural space is relatively easy and safe. Unlike the peritoneal cavity, where adhesions and inflammation can cause severe complications, fusion of the pleural space is quite benign, and in some instances (i.e. symptomatic pleural effsions) may be desirable.

Goals for gene therapy of the pleural space

Gene transfer to the pleural space could be employed in at least two possible scenarios. First, the cells of the pleural space could be used as factories to produce missing or defective gene products that would be secreted and then transferred into the systemic circulation. There are a number of diseases, such as hemophilia, α1AT disease, some lysosomal storage disorders or diabetes, where regulated or unregulated secretion of difficult-to-produce protein products would be advantageous. Second, gene therapy could be utilized in the treatment of pleural diseases. In this context, the primary objective would be to treat pleural malignancies, including primary tumors (MM) and secondary, metatstatic tumors. It seems less likely that gene therapy will play an important role in most other pleural diseases since they are usually secondary to infections and other lung or systemic diseases.

Vectors used in pleural gene therapy

The first requirement for successful gene therapy is efficient gene delivery and a variety of viral and nonviral gene transfer vectors have been developed [42,43]. As summarized in Table 17.1, each of these vectors has certain advantages with regard to DNA carrying capacity, types of cells targeted, *in vivo* gene transfer efficiency, duration of expression and induction of inflammation.

Retroviruses

The principal advantages of this vector derive from its availability to accomplish efficient gene transfer *in vitro* in a broad range of targeted cells, with the capacity to achieve integration into the host genome and long term expression. However, the

Table 17.1 Properties of various gene therapy vectors.

	Retrovirus	*AAV*	*Adenovirus*	*Liposomes*
Genome	RNA	ssDNA	dsDNA	N/A
Transgene size (Kb)	9.6	4.8	36.0	Unlimited
Nondividing cells	Y	Y	Y	Y
Integration	Y	Y/N	N	N
Duration of expression	L	L	S	S
Preexisting immunity	N	Y	Y	N
CTL response	N	N	Y	N
Efficiency of gene transfer	Modest	Modest	High	Low
Safety issues	Insertional mutagenesis	Insertional mutagenesis	Inflammation	Minimal

L, long; N, no; N/A, not applicable; S, short, Y, yes.

packaging capacity of the virion is limited and the vectors can achieve gene transfer only to dividing cells. Moreover, these vectors are labile *in vivo* since complement and other components can inactivate the virion. The requirements for cell proliferation and *in vivo* lability have severely limited the utility of these agents in the context of direct *in vivo* delivery applications.

Retroviruses have been used to transduce mesothelial cells in culture for subsequent reinjection (see later) and this will likely be their most useful role in pleural gene therapy [44]. Successful use of retroviruses for *in vivo* transduction into the pleural and peritoneal space has been limited. Concentrated vector encoding a suicide gene has been reported to treat cancer cells in the peritoneal cavity [45]. Use in malignant pleural disease may be limited by the presence of chondroitin sulfate proteogylcans/glycosaminoglycans that appear to inhibit retroviral gene transfer [46].

Adeno-associated virus

Another viral vector that has generated tremendous interest is the adeno-associated virus (AAV), a defective parvovirus with a single strand DNA genome and a naked protein coat [47]. AAV has not been associated with any known human disease state, suggesting a significant safety margin for this vector. In addition, after wild-type AAV entry to the host cell, there is a site-specific DNA integration step. It appears that recombinant vectors do not retain this integrative capacity, but do seem to persist in an episomal state that allows for stable, long term gene expression while potentially circumventing the safety concerns surrounding an integration event. To date, there have been no published reports of AAV-mediated gene therapy in human pleural diseases.

Adenoviruses

The most widely used vector system in pleural gene therapy has been replication-incompetent recombinant adenovirus. Recombinant adenovirusal vectors have deletions of crucial viral genes needed for replication, and are produced by packaging cell lines that provide these functions *in trans.* [48]. The deleted gene regions can then be replaced with expression cassettes containing the desired gene under the control of general or tumor specific promoters. This vector system offers a number of advantages including high efficiency transduction of target cells (including nondividing cells) and high expression levels of the delivered transgene [49]. The two primary disadvantages of adenoviruses in traditional gene therapy are that they result in only transient gene expression and that, when employed for direct *in vivo* applications, the virions elicit a prominent local and systemic inflammatory response [50]. However, the induction of intratumoral inflammation leading to a more "immunostimulatory" environment may be a distinct advantage for many types of cancer gene therapy.

Mesothelial and mesothelioma cells in culture are quite easily transduced by adenoviral vectors. More importantly, these vectors have been injected

into the pleural and peritoneal spaces in animal models where uniform and high level gene transduction occurs [51–53]. Despite reports of soluble factors in pleural fluid of MPEs that inhibit adenoviral gene transfer [54], our group has injected adenoviral vectors into the pleural space of patients with MM and showed clear gene transfer of tumor and normal mesothelial cells by detection of transgene DNA, RNA and protein at three days after vector instillation (see later) [55]. Clinical trials using i.p. injection of adenoviral vectors for the treatment of ovarian cancer have also proved safe with some evidence of gene transfer [56]. Thus, adenoviral vectors can be used in humans to transfer genes, at least transiently, into pleural and peritoneal mesothelial cells.

Nonviral vectors

As an alternative to viral vectors, a variety of nonviral vectors have also been developed for *in vivo* and *in vitro* gene delivery. Several general strategies have been developed to achieve this end, including liposomes and molecular conjugates.

Liposomes are artificial lipid bilayers designed to translocate drugs or nucleic acids into the cell cytosol via a cell-membrane fusion event or endocytosis [57]. The basis of transduction is interaction of a DNA/lipid complex with target cell membranes to allow translocation to cell cytosol. For the most part, liposomal/DNA complexes appear to be less efficient than the various viral vectors described earlier and they do not result in prolonged transgene expression. Nonetheless, their design offers certain potential advantages, including simplicity of construction, enhanced DNA packaging capacity, lessened safety concerns and the potential for targeted gene delivery that warrant their further development.

There have been a number of studies utilizing liposomes for i.p. gene transfer, primarily for treatment of cancer. These studies have shown successful gene transfer into tumor cells along with varying degrees of tumor inhibition. Pleural gene transfer to treat a model of metastatic pleural disease using liposomes has also been reported [58]. Toxicology studies have shown the relative safety of this approach [59], and, in fact, a Phase I trial examining the use of IP and i.p. injection of liposomes containing the adenoviral E1A transgene into patients with metastatic cancer of the breast or ovary has been completed [60].

Gene therapy for the treatment of systemic diseases

The large surface area of the pleural space, the observation that mesothelial cells in culture have considerable secretory potential, the fact that the pleural space mediates exchange of solutes between the blood and lymph and the relatively easy access to the pleural space has raised the possibility of using gene therapy to the pleural space for the treatment of systemic diseases [61,62].

Although an attractive idea, so far this approach seems limited for use in short term therapy where production of a biologically active protein for a brief period of time (i.e. days) would be advantageous. Setoguchi *et al.* delivered a replication-deficient adenovirus encoding human α1AT to cotton rats intraperitoneally. Human α1AT was detectable in the serum at 4 days at a respectable concentration of 3.4 μg/mL. Unfortunately, expession levels rapidly declined (levels were back to baseline by 24 days) and repeat dosing was ineffective [63]. A significant but transitory level of expression of an ectopic protein was also seen when naked plasmid DNA was instilled into the pleural space of rabbits [64]. This rapid loss of expression and inability to readminister vector highlights the potential problems of using adenovirus or naked DNA. Similar problems with short duration of expression would be seen with liposomal approaches. However, one could image scenarios where rapid and constant production of a protein might be useful for limited periods of time. For example, during sepsis, production of inhibitors of specific cytokines (i.e. interluekin-1 receptor antagonists) or antioxidants could be useful.

There is no human data available yet to show the feasibility of using gene therapy for long term treatment of deficiency diseases. In this scenario, potentially useful vectors might be AAV or lentiviruses. In fact, in a murine model, AAV-human-α1AT constructs were instilled into the pleural space and resulted in significantly higher

serum and pleural concentrations of human α1AT compared to intramuscular AAV treatment. Most importantly, at 40 weeks post-administration, IP administration of the AAV5-human-α1AT vector-mediated serum α1AT levels of 900 $\pm$50 μ g/mL, 1.6-fold higher than the accepted therapeutic level of 570 μg/mL [65]. This data suggested that the appropriate vector may allow the pleural mesothelial cells to become a persistent factory for the production of deficient proteins. Another issue that would need to be addressed is how long the transfected mesothelial cells would remain alive and secretory. Transduction of cells *ex vivo* followed by injection into the pleural space could also potentially be useful to treat systemic diseases if long term secretion could be achieved. However, as discussed earlier, currently only short term secretion has been obtainable with this approach.

Nonmalignant pleural diseases

It is currently difficult to envision a large number of clinical scenarios where pleural gene therapy would be both useful and cost-effective. The two large classes of nonmalignant pleural diseases are those related to lung or pleural infection and those secondary to underlying systemic diseases (i.e. congestive heart failure), neither of which is particularly amenable to local therapy.

The primary therapeutic procedure to the pleural space is sclerosis. Although instillation of adenovirus clearly led to pleural inflammation and fusion of the pleural space in our clinical trial for mesothelioma [55], this approach is unlikely to be cost effective. One could imagine a situation, however, e.g. refractory air leaks, where it could be beneficial to introduce a gene (i.e. platelet-derived growth factor) that might accelerate healing.

Malignant pleural diseases

In the near future, the most likely use for pleural gene therapy will be in the treatment of malignant diseases including MM and metastatic pleural disease. Pleural tumors have several characteristics that make them attractive targets for gene therapy, including: (a) the absence of standard, effective therapy; (b) its accessibility in the pleural space for biopsy, vector delivery and analysis of treatment effects; and (c) the susceptibility to therapeutic strategies offering only transient gene expression. MM is an especially attractive target since local extension of disease, rather than distant metastases, is responsible for much of its morbidity and mortality. Accordingly, a large number of animal studies and some clinical trials have been performed using gene therapy approaches.

Several different cancer gene therapy approaches are currently being explored for malignant pleural tumors including use of so-called suicide genes, delivery of tumor suppressor genes and transfer of immunomodulatory genes.

Suicide gene therapy

One prominent approach in cancer gene therapeutics is the so-called suicide gene therapy where a neoplasm is transduced with a cDNA encoding for an enzyme rendering tumor cells sensitive to a "benign" agent, by converting the "prodrug" to a toxic metabolite. The enzyme used most commonly is the herpes simplex virus-1 thymidine kinase (HSV*tk*) gene, which when incorporated into malignant cells renders them sensitive to the nucleoside analog ganciclovir (GCV) and induces cell killing [66]. Therapeutic efficacy is enhanced by the finding that transgene expression in every cell is not required for complete tumor regression. This so-called bystander effect is complex and appears to involve passage of toxic GCV metabolites from transduced to non-transduced cells via gap junctions or apoptotic vesicles [67,68] and/or induction of antitumor immune responses capable of killing tumor cells not expressing the HSV*tk* transgene [69]. The transfer of HSV*tk* DNA to target tumor cells has been accomplished in a variety of ways including the use of cellular delivery systems, liposomes and viral vectors.

One approach, first proposed by Kolls *et al.* in 1998, was to transduce tumor cells *ex vivo* with HSV*tk* and inject them into the peritoneal or pleural cavity. Treatment with GCV was shown to induce the death of the transduced cells accompanied by a powerful bystander effect which was amplified by release of immunostimulatory cytokines that led to killing of non-transduced cells [70]. This approach has been directly tested in mouse models of i.p. MM. Kolls *et al.* (1998) showed that

injection of an HSV*tk*-transduced ovarian cancer cell line (PA1) into mice with established MM followed by GCV treatment led to a marked increase in survival [70].

Based on these studies, a cell-transfer trial has been conducted by Schwarzenberger and colleagues at the Louisiana State University (LSU) Medical Center in New Orleans. The protocol consisted of the IP instillation of an irradiated ovarian carcinoma cell line retrovirally transfected with HSV*tk* (PA1-STK cells) via an indwelling pleural catheter followed by systemic administration of GCV [71]. In patients treated to date, minimal side effects have been seen, while preliminary findings show significant posttreatment increases in the percentage of CD8 T-lymphocytes in pleural fluid; however, no clinical responses have been noted [72]. Interestingly, the LSU investigators have also demonstrated that PA1-STK cells home to MM deposits in patients after IP instillation [51].

Direct transduction with the HSV*tk* gene of tumor cells growing within the peritoneal or pleural cavity has also been achieved. Antitumor effects of the HSV*tk* gene followed by treatment with GCV have been seen using concentrated retroviral supernatants, liposomes and plasmid DNA : polyethylenimine complexes [58,73].

The most effective and most carefully studied vector, however, has been adenovirus. Initial experiments demonstrated that replication-deficient adenoviral HSV*tk* vectors (Ad.HSV*tk*) efficiently transduced mesothelioma cells both in tissue culture and in animal models and facilitated HSV*tk*-mediated killing of human mesothelioma cells in the presence of low concentrations of GCV [74,75]. Subsequently, Ad.HSV*tk*/GCV gene therapy was used successfully to treat established, i.p. human MM tumors and lung cancers in immunodeficient mice [76,77] and in rat models of MM [53,68].

Based on success in animal models, Sterman *et al.* conducted a Phase I clinical trial of a replication-incompetent adenoviral vector encoding HSV*tk* (Ad.HSV*tk*) delivered intrapleurally into 21 patients with MM [55,78]. After vector instillation, patients were treated with 2 weeks of systemic GCV. Dose limiting toxicity was not reached, side effects were minimal and gene transfer was confirmed in 11 of 20 evaluable patients in a dose-related fashion with clearly detectable gene transfer (evidenced by immunostaining) at tumor surfaces and up to 30–50 cell layers deep. Strong anti-adenoviral immune responses, including high titers of neutralizing antibody and proliferative T-cell responses were generated [55]. A second trial was reported investigating the use of systemic corticosteroids to mitigate anti-vector immune responses. A similar group of patients as previously described was treated with vector plus high dose corticosteroids for 3 days. In comparison with patients treated with the same dose of IP Ad.RSV*tk*, steroid-treated patients demonstrated decreased localized and systemic inflammatory responses and showed a trend toward increased intratumoral gene transfer. Intravenous methylprednisolone failed to inhibit the generation of anti-Ad antibodies or Ad-induced peripheral blood mononuclear cell activation [79]. Although limited by the small numbers of patients studied, the data indicated that administration of systemic steroids was safe and may limit acute clinical toxicity; however, these agents are not likely to significantly inhibit cellular and humoral responses to adenoviral vectors. Despite the fact that these were Phase I trials, some clinical responses were seen; 2 patients remained tumor free 3 years after treatment and partial tumor regression was observed in a number of the patients receiving the higher doses of vector.

An additional 8 patients were treated with a slightly modified Ad.HSV*tk* virus that had a lower incidence of recombination to form wild-type virus. Of the 8 patients treated in this second Phase I trial, there are 2 surviving, both of whom were treated at the higher dose level of 5.0×10^{13} particles of Ad.HSV*tk*. Both had clinically and radiographically SD without other antitumor therapy for 6 years after treatment. There was no significant difference in side effect profile compared to the previous trial.

Our clinical data showing limited toxicity, detectable gene transfer, as well as our anecdotal experience with tumor responses, suggested the Ad.HSV.*tk*/GCV approach has exciting potential for the treatment of MM, as well as other localized malignancies. Using the current strategy, therapeutic efficacy could only be expected in patients with relatively small tumor loads (small nodules or diffuse, "thin" tumors). An alternative treatment schema would involve surgical "debulking" to

minimize tumor burden, followed by administration of Ad.HSV*tk* as an adjuvant therapy. Another method of improving intratumoral gene transfer would be repeated administration of vector and GCV (i.e. three doses over a 3-week period), use of artificially enhanced HSV*tk* mutants [80] or the use of adenoviral vectors capable of selective replication in mesothelioma cells.

Cytokine gene therapy

There has been significant interest at many centers in the delivery of genes encoding cytokines to the pleural space of patients with MM. The rationale for this approach is that expression of cytokine genes by tumor cells generates a high level of intratumoral cytokines in paracrine fashion, inducing powerful local cytokine effects without significant systemic toxicity. Prolonged local cytokine expression can induce activation of tumor-infiltrating dendritic cells (DCs) to express MHC-tumor antigen complexes in conjunction with co-stimulatory molecules. These activated DCs can then migrate to regional lymph nodes where they stimulate proliferation of tumor specific CD8 and CD4 lymphocytes, inducing antitumor cytotoxicty at distant sites of tumor. In addition, some pro-inflammatory cytokines such as IL-2 have the capability of direct intratumoral activation of $CD8^+$ tumor infiltrating lymphocytes, overcoming tolerance signals to produce tumor-specific CTLs. Increased intratumoral IL-2 may also activate NK cells and LAKs. Animal experiments have shown that injection of IL-2-transduced tumor cells increases specific antitumor activity, generates systemic responses to the parental tumor augments the immune response against autologous tumor and causes rejection of rechallenged tumor cells [81,82]. This approach has obvious appeal for metastatic pleural disease where local treatment would offer the possibility of systemic immune responses.

One reason for enthusiasm for cytokine gene therapy in MM is that exogenous cytokines are known to have both direct antiproliferative effects upon mesothelioma cells, as well as activating IP and intratumoral immune effector cells *in vivo*. Several published Phase I and Phase II clinical trials have documented mesothelioma tumor responses to IP infusion of IL-2, interferon-β (IFN-β) and IFN-γ [23–26,29]. In particular, IP IFN-γ has demonstrated a significant response rate in pleural mesothelioma, with several CRs in patients with Stage IA disease (tumor limited to the parietal and diaphragmatic pleual surfaces) [25,26]. See (Interapleural immunotherapy)

The first human clinical trial of direct intratumoral delivery of cytokine genes in malignant pleural mesothelioma was conducted by investigators at Queen Elizabeth II Hospital in Perth, Australia, using a recombinant vaccinia virus (VV) expressing the human IL-2 gene. A vaccinia vector was chosen because of its large genome, proven safety in human vaccines and availability of anti-VV antibodies for evaluation of vector-induced immune responses. In addition, insertion of the IL-2 gene into the thymidine kinase region of the VV theoretically rendered it partially replication-restricted, allowing for relatively more expression in tumor cells. The VV–IL-2 vector at a dose of 1×10^7 pfu was serially injected into palpable chest wall lesions of six patients with advanced MM. Toxicities were minimal, and there was no clinical or serological evidence of spread of VV to patient contacts. No significant tumor regression was seen in any of the patients, and only modest intra-tumoral T-cell infiltration was detected. VV–IL-2 mRNA was detected by reverse transcriptase-PCR in serial tumor biopsies for up to 6 days after injection, but declined to low levels by day 8 [83]. The prolonged nature of IL-2 gene expression in this trial was remarkable considering the fact that significant serum titers of anti-VV neutralizing antibodies were generated in all patients.

Several other candidate cytokine genes are being evaluated for therapeutic effectiveness in animal models of MM. Caminschi and colleagues at Queen Elizabeth II Medical Center in Perth have investigated genetic alteration of murine mesothelioma cell lines with the gene for interleukin-12 (IL-12), one of the most active immunomodulatory cytokines [84]. This same group previously demonstrated that systemic administration of exogenous IL-12 induced strong antitumor immune responses in mice bearing syngeneic mesothelioma tumors [85].

The type I (α, β) and type II (γ) interferons have been shown to have clinical antitumor activity when administered exogenously to patients

with MM. IFN-β, e.g. has potent antiproliferative *in vitro* effects on mesothelioma cells, and strong immunostimulatory actions in animal models, but is limited in clinical use by toxicity of systemic administration [86]. Our group has therefore investigated the effects of IFN β-gene therapy in murine models of MM showing that a single i.p. injection of a recombinant adenovirus engineered to express the murine β-interferon gene (Ad.muIFN-β) can eradicate syngeneic murine MM in more than 90% of animals tested [87]. i.p. Ad.muIFN-β gene therapy resulted as well in significant reduction of subcutaneous tumors at a distant site. These effects of Ad.muIFN-β were clearly shown in several experiments to be mediated by CD8+ T-lymphocytes.

Based upon this exciting preclinical data, we developed a Phase I clinical trial whereby an adenoviral vector expressing IFN-β is instilled into the pleural space of patients with mesothelioma or metastatic pleural disease (10 patients). Our primary endpoint to demonstrate safety of IP adenovirus delivery has been achieved with minimal toxicity – one patient with transient hypoxemia and one patient with self-limited mild transaminitis. Interestingly, one patient with ovarian cancer demonstrated disease regression, and one patient with sarcomatoid mesothelioma and one patient with epithelial mesothelioma have demonstrated stability of disease as measured by CT scan and position envision tomography (PET) scan 60 days following treatment. Immunologic analysis of the patient with ovarian cancer demonstrated the development of a cytolytic immune response following IP IFN-β as measured by a chromium release assay. This patient also developed a new immunologic response against an antigen in a Western blot following treatment. The immunologic analysis of this trial is ongoing at this time. Therefore, it appears IP gene therapy with immune modifying agents is well tolerated with the potential for significant clinical and immunologic responses. We plan to perform another Phase I trial with multiple IP dosings of IFN-β, followed by Phase II trials combining immunotherapy with chemotherapy.

Induction of apoptosis

One of the primary approaches to cancer gene therapy research over the past decade has been mutation compensation – the replacement of absent or mutated tumor suppressor genes responsible, at least in part, for the malignant phenotype of the cancer cell. Intratumoral delivery of the wild-type p53 gene, e.g. has been the most frequent method of experimental gene therapy of solid tumors, as mutations in the p53 tumor suppressor gene account for the majority of genetic abnormalities in solid tumors. Most MM, however, contain wild-type p53 and a normal copy of the cell cycle regulator retinoblastoma (pRB). The most common molecular abnormality found in MM is absent expression of the cyclin-dependent kinase (cdk) inhibitor, $p16^{INK4a}$. This mutation can lead to unmitigated progression through the cell cycle despite the presence of normal pRB expression and wild-type p53, and therefore the development of a neoplastic phenotype [88,89].

Frizelle and colleagues at the University of Minnesota School of Medicine have demonstrated that reexpression of $p16^{INK4a}$ in mesothelioma cells *in vitro* and *in vivo* results in cell cycle arrest, cell growth inhibition, apoptosis and tumor reduction [89]. In addition, these investigators have recently shown that repeated administration of an adenoviral vector expressing wild-type $p16^{INK4a}$ into established human mesothelioma xenografts in nude mice resulted in prolongation of survival compared with controls receiving saline or an Ad vector expressing the marker gene *lac Z* [88]. Successful application of this technology to human clinical trials is dependent upon the development of more efficient means of tumor cell transduction.

Investigators at the Thoracic Oncology Laboratory, University of California, San Francisco Cancer Center, are targeting another common mutation in MM for mutation compensation gene therapeutic approaches. Yang and colleagues at UCSF have demonstrated that homozygous deletion of the INK4a/ARF locus is common in human MM. The p14 (ARF) protein encoded by the INK4a/ARF locus promotes degradation of the MDM2 protein and thus prevents the MDM2-mediated inhibition of p53. Deletion of the INK4a/ARF locus, therefore, may abrogate p14 (ARF) protein expression, thereby inactivating p53 (via MDM2), and leading to unchecked progression through the cell cycle. The UCSF team

transfected human mesothelioma cell lines with an adenoviral vector encoding for human p14 (ARF) cDNA (Adp14). Over-expression of p14 (ARF) within the mesothelioma cells led to increased amounts of p53 and p21, and dephosphorylation of pRb. In addition, Adp14 inhibited mesothelioma cell growth via induction G(1)-phase cell cycle arrest and apoptotic cell death [90]. To date, this approach has not yet been tested in human clinical trials [66].

Interestingly, Yang's group have also investigated the efficacy of the ONYX-015 adenovirus in mesothelioma cells, and found that the cytolytic effect of this agent in mesothelioma is dependent upon absence of p14 (ARF) expression [91]. ONYX-015 is a conditionally replication competent adenovirus lacking the E1b55kDa gene, and therefore can only replicate in tumor cells lacking functional p53. (One of the functions of E1b55kDa is to bind and inactivate wild-type p53.) Clinical trials of ONYX-015 in patients with cancers of the head and neck and lung have shown evidence of tumor reduction with minimal toxicity [92,93]. As described earlier, in mesothelioma, unlike many other solid tumors, genetic alterations in p53 are uncommon, but functional inhibition of p53 can be achieved via deletions in the INK4a/ARF locus. The UCSF group demonstrated *in vitro* cytotoxicity of ONYX-015 on mesothelioma cell lines lacking p14 (ARF), and increased resistance of these same cell lines to ONYX-015 after transfection of the tumor cells with Adp14 [91].

Despite the fact that most mesotheliomas have wild-type p53 (wt-p53), the function of p53 in mesothelioma cells may be abnormal secondary to binding of p53 by inhibitor proteins such as mdm2 and SV40 large T antigen. Therefore, there may be a rationale for gene therapy of mesothelioma via over-expression of wt-p53 within the cell. Giuliano and colleagues in Chieti, Italy, performed a series of experiments in which they transfected human mesothelioma cells with a replication-deficient adenoviral vector carrying the wt-p53 gene. They demonstrated greater than 80% inhibition of tumor cell growth *in vitro* at a multiplicity of infection (MOI) of 25 with documentation of induction of apoptosis in the dying tumor cells. In addition, Giuliano and colleagues showed that *ex vivo* transfer of the wt-p53 gene to mesothelioma cells inhibited growth of tumor implants in nude mice. In immunodeficient mice with established human mesothelioma xenografts, intratumoral injection of the wt-p53 gene inhibited tumor growth and prolonged survival [94]. It is not inconceivable, therefore, to consider human clinical trials of Ad. wt-p53 gene therapy in mesothelioma akin to those conducted in lung cancer, head and neck cancer and metastatic colon cancer.

An alternate method of inhibiting mesothelioma cells is the introduction of "downstream" promoters of apoptosis such as the pro-apoptotic Bcl-2 family member Bak. Pataer and colleagues at M.D. Anderson Cancer Center in Houston co-delivered binary adenoviral-Bak/GV-16 vectors into wt-p53 positive and mutated p53 mesothelioma cell lines *in vitro*, along with binary Ad.*lacZ*/GV-16 control vectors [69]. The M.D. Anderson group demonstrated marked induction of apoptosis and decreased cellular viability in both p53 "sensitive" and "resistant" cell lines with Bak gene transfer, but not with *lacZ* delivery [95]. Thus, gene transfer *in vivo* with pro-apoptotic Bcl-2 family members would be a reasonable strategy for future mesothelioma gene therapy clinical trials.

Another gene that has been used to induce apoptosis, downregulation of the HER-2/neu oncogene and differentiation in a wide variety of tumor cells is the adenovirus E1A gene [96]. Based on preclinical studies, a clinical trial using direct IP or i.p. injections of a liposome encoding the Ad E1A gene was recently completed [60]. E1A gene expression in tumors was detected and some increased apoptosis and reduced proliferation of cells were noted. Toxicities that limited the dose were fever, nausea and vomiting and/or discomfort at the injection site. Further trials are in the planning stages.

Conclusions

Pleural gene therapy could potentially be used to treat systemic diseases by providing a large and easily accessible cellular target for gene transduction and protein secretion or for the treatment of a number of pleural diseases. Preclinical studies have shown that *ex vivo* or direct *in vivo* transduction mesothelial cells is feasible and allows for large amounts of proteins to be produced locally and in

the systemic circulation for short periods of time. In the next decade it is likely that the use of this ability for transient expression and the development of vectors that will allow long term production of therapeutic proteins will make pleural gene therapy a potentially useful tool to treat deficiency diseases such as hemophilia.

The other area where pleural gene therapy is likely to become useful is in the treatment of pleural diseases, especially pleural malignancies. A number of clinical trials in cancer patients have been completed that show the safety and feasibility of this approach. Pleural immunotherapy for treatment of MM and metastatic pleural disease is an especially promising area.

To date, gene therapy has not been proven as a useful therapeutic tool for the treatment of pleural diseases. However, the field is less than 15 years old and great initial progress has been made. It is likely that gene therapy will be an important treatment strategy in the near future.

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PART IV

Case discussions

18 CHAPTER 18

Management of patients at increased risk for lung cancer

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Introduction

The American Cancer Society (ACS) estimates that in 2002 there will be an estimated 169 400 new cases of lung cancer, and there will be an additional 154 900 lung-cancer-related deaths [1]. While the trend in lung-cancer-related deaths looks to have peaked and appears to be in a slight decline, there still remains a significant population at risk of developing lung cancer. The primary risk factor for developing lung cancer is cigarette smoking and is directly related to the quantity and duration of tobacco use, although this risk declines slowly over time if smoking is stopped. Even as the prevalence of tobacco smoking in the United States continues to decline, the percentage of the population who continues to smoke remains high [2]. As of the year 2000 there were an estimated 46.5 million U.S. adults (23.3% of the population) actively smoking and an additional 44.3 million were former smokers [3]. There are two populations of individuals at increased risk for developing lung cancer. The largest group is asymptomatic current and ex-smokers with evidence of airflow obstruction on spirometry [4]. The smaller group is patients post resection of limited-stage (I and II) non-small cell lung cancer; this group is at increased risk for developing metachronous primary lung cancer as well as recurrent disease [5,6]. Review of the data supporting screening trials in each of these groups will be discussed separately.

Survival after diagnosis of lung cancer is directly related to the stage at the time of diagnosis. As would be expected the 5-year survival rates for the earlier stages of lung cancer remain disproportionately higher than those cases diagnosed at later stages (Table 18.1) [7,8]. Stage IA disease offers the greatest potential for long-term disease-free survival; unfortunately this group represents only 13% of patients at diagnosis. Screening tests for lung cancer would ideally allow for diagnosis at an earlier stage and therefore improve lung-cancer-related mortality. Despite this, ACS guidelines regarding the early detection of cancer states that "…the ACS does not recommend testing for early lung cancer detection in asymptomatic individuals at risk for lung cancer" [9]. The ACS guidelines do allow for patients at increased risk of lung cancer to undergo early cancer screening at their physician's discretion [10]. "At a physician's discretion" leaves open the practice of "looking" for cancer in a non-uniform unsupported manner. Screening methods that have shown promise include conventional chest roentgenography, spiral computed tomography (CT) and autofluorescence (AF) bronchoscopy.

Table 18.1 Survival rates (cumulative percentage surviving) in different stages [7].

Stage	*No. patients*	*Time after treatment, mo.*				
		12	*24*	*36*	*48*	*60*
IA	416	94	83	76	69	53
IB	833	85	68	59	52	46
IIA	84	90	72	61	57	52
IIB	678	74	54	43	37	33
IIIA	350	63	36	28	22	19

Screening

Screening for any cancer is based on the premise that detection of cancer, at an asymptomatic early stage where curative therapy can be performed, should be associated with a reduction in cancer-specific mortality. Screening has been used successfully in other cancers (breast [11], colorectal [12]) to decrease cancer-specific mortality. However, screening for breast cancer has recently become controversial given the results of several new studies and meta-analyses of prior trials. In particular, the survival benefits of breast cancer screening by mammography and clinical breast self-examination have been recently called into question. Meta-analyses of mammography trials did not demonstrate any mortality benefit from screening [13,14], and well-done trials of mammography in 40–49 and 50–59 year-old women in Canada did not demonstrate any mortality reduction with mammography screening [15,16]. Similarly, a large trial examining clinical breast self-examination did not demonstrate any reduction in breast-cancer-specific mortality [17]. Adding to the controversy, the U.S. Preventive Services Task Force performed its own meta-analysis that did demonstrate a breast-cancer-specific mortality reduction from mammographic screening and continues to recommend it for women after the age of 40 despite a well done trial to the contrary [18].

Several biases can occur in cancer screening that can make screening appear beneficial when there is actually no cancer-specific mortality reduction. These can be divided into patient and disease process biases. Most lung cancer screening trials enroll patients who "volunteer" for the study, causing a selection bias by screening a population who may not be representative of the actual population at risk, limiting the potential validity of the trial results. Often these volunteer populations are either healthier or have specific risk factors not found in the more general population. The most common disease process biases are: lead-time bias, length-time bias and over-diagnosis bias. Lead-time bias is where the screening process does not lead to any change in the diseases natural history; i.e. early detection causes an apparent increase in survival time but does not actually alter the course of the disease or increase patient survival. Length-time bias can be exemplified by the spectrum of tumor aggressiveness, with less aggressive tumors that are diagnosed due to screening tests often having a longer patient survival time, whereas more aggressive tumors diagnosed due to development of symptoms usually have a shorter patient survival time, yet often without any actual difference in lung-cancer-specific mortality. Over-diagnosis bias is the extreme of length-time bias where slow-growing tumors are detected early, but are not fatal secondary to their indolent nature. Of all the forms of bias that may be present in screening, lead-time bias may be the most difficult to account for.

Roentgenographic screening

There have been several randomized population controlled trials that have examined the survival benefits of chest roentgenographic screening for early lung cancer detection [19–24]. The results of these studies form the basis for the "no screening" recommendation of the ACS. The Memorial Sloan-Kettering [19,24] and Johns Hopkins [22] studies examined the additive benefit of sputum cytology to annual chest roentgenographic examination and did not evaluate the lung cancer mortality reduction benefit of chest roentgenographic screening alone, and will not be included in this discussion. Due to the questions regarding sputum cytology we have chosen not to address it here. Of the radiographic studies, the Mayo Lung Project represents the best attempt at comparing an intensive chest roentgenogram screening program with sputum cytology (chest roentgenogram and 3-day pooled sputum every 4 months) as compared to a standard clinical practice group (annual chest roentgenogram recommended with annual sputum cytology advised) [20]. When the results of the screening study were published the intensive screening group had a statistically increased incidence of lung cancer and lung cancer mortality as compared to the control group. The authors did not recommend further intensive screening. A similar screening study was carried out in Czechoslovakia, with patients undergoing prevalence (baseline) chest roentgenogram screening and subsequent randomization to either chest roentgenogram every 6 months for 3 years or to

a follow-up chest roentgenogram at the end of the 3-year study. There was no lung-cancer-specific mortality benefit to the intensive screening group as compared to the control group, and similar to the Mayo Lung Project data the intensive screened group had a higher incidence of lung cancer [23].

G.M. Strauss recently reanalyzed the Mayo Lung Project data. Survival time from diagnosis of lung cancer, randomization and diagnosis by method of detection were all statistically significant in favor of the screened cohort [25]. This suggests that radiographic screening using simple chest roentgenography may offer a survival benefit, reopening the question of the use of this inexpensive method for general screening of high risk populations.

Computed tomography screening

Computed tomography of the chest offers the ability to for higher resolution screening of the chest and the earlier detection of lung cancer in individuals at risk. Several investigators have recently evaluated the use of low-radiation-dose spiral CT as a screening tool for the early detection of lung cancer. The Early Lung Cancer Action Project (ELCAP) and the Mayo Clinic CT lung screening study were the most comprehensive published attempts at evaluating the role of low-dose spiral CT of the chest in the early detection of lung cancer. Both of these trials are prospective cohort studies examining the sensitivity of detection at early stage of lung cancer and unfortunately do not address the most important question, that of lung-cancer-specific mortality reduction due to early detection by the use of screening CT.

The ELCAP baseline screening (prevalence) study was reported in the *Lancet* in 1999 [26]. One thousand individuals considered at increased risk for lung cancer underwent spiral CT of the chest. Twenty-seven of these patients (2.7%) were found to have malignancy. Spiral CT identified all 27 patients with malignancy and was found to be superior when compared to conventional chest roentgenogram, which only detected 7 (0.7%) of the malignancies. An impressive 85% ($n = 23$) of spiral CT detected malignancies were Stage I versus 15% ($n = 4$) by chest roentgenogram. It is a matter of concern that of the individuals screened, 233 were found to have non-calcified pulmonary nodules (NCN) detected on the baseline spiral CT scan. The majority then required high-resolution chest CT for further characterization and then biopsy or subsequent interval high-resolution CT with biopsy if warranted by the diagnostic algorithm employed by the investigators. Only 68 of the 233 NCN detected by spiral CT were detectable by chest roentgenogram.

The Early Lung Cancer Action Project has now reported the results of the first repeat (incidence) screening tests [27]. Of the 1000 originally evaluated patients, 841 of the enrolled individuals had undergone annual (6–18 months after initial screen) spiral CT screening. An additional 343 CT scans were performed 6–18 months after the most previous scan, allowing for review of 1184 annual screening CT scans. Of the 1184 annual screening CT scans performed, positive findings, defined as newly detected NCN, and were present in 63 patients. Upon comparison with prior scans, 23 of the NCN were identified retrospectively (having been missed on the prior study) and did not demonstrate interval growth and were determined to be stable. Ten NCNs were determined to be negative on high-resolution CT scanning and 12 had resolved by the 1-month high-resolution CT scan. Of the remaining patients, 2 died of cardiac causes and 16 required additional diagnostic studies. Eight patients were followed radiographically and were found to be stable. The remaining 8 all underwent biopsy and were diagnosed with malignancy: 7 Stage IA and 1 Stage IIIA (despite primary lesion of 5 mm) lung cancers. During the interim period there were 2 additional malignancies diagnosed due to new symptom development. Both of these cases were found to have endobronchial disease not visualized by baseline screening spiral CT scans.

Swensen *et al.* at the Mayo Clinic recently reported their data from a prospective cohort study on the prevalence and first incidence screening using spiral CT and sputum cytology [28]. One thousand five hundred twenty patients more than or equal to 50 years of age and with a more than or equal to 20-pack-year smoking history were enrolled to undergo prevalence spiral CT screening and sputum cytology followed by annual spiral CT and sputum cytology. On prevalence CT screening 51% of patients had at least one non-calcified

pulmonary nodule identified; there were 22 lung cancers identified during prevalence screening with 12 (57%) being Stage IA non-small cell lung cancer. Seven of the nodules resected were found to be benign. At the first annual incidence spiral CT and sputum cytologic screening there were 1464 patients (97%) that underwent follow-up studies. Of those screened, at least one non-calcified pulmonary nodule was identified in 66% of patients. Of this 66%, there were three incidence lung cancers detected (a limited small cell, a IIA and IIB non-small cell lung cancers). The point of concern that should be apparent here is that the non-small cell lung cancers found at incidence screening were not early IA but rather more advanced disease.

Diederich *et al.* published a comparable prevalence study in individuals at risk for lung cancer, but has not yet reported incidence data [29]. Eight hundred seventeen people were enrolled and underwent baseline screening by spiral CT. Forty-three percent of patients ($n = 350$) had NCN and underwent additional high-resolution CT screening according to their algorithm. Twelve malignancies were identified on biopsy in 11 individuals (1.3%). There were 3 benign lesions biopsied in this study. Stage IA disease was diagnosed in 7 of the 11 patients.

Sone *et al.* examined the effect of spiral CT screening for early lung cancer detection on a cohort of patients and has reported on baseline screening (prevalence) and 2 years of annual screenings (incidence) [30]. Fifty-four percent of the individuals screened were never-smokers, which differs with ELCAP and the Mayo Clinic data. The Sone publication is notable for raising the possibility of false negative CT readings, given one negative spiral CT with positive sputum cytology during the prevalence study. The authors identified a total of 17 false negative CT studies over the 3 years of screening with on retrospective review of CT scans after symptomatic diagnosis of malignancy.

Spiral CT screening for the early detection of lung cancer has significant appeal for the increased sensitivity over conventional chest roentgenography. However, despite the encouraging results from prevalence studies, as well as the first annual incidence report of ELCAP and the Mayo project, there is no data to suggest a disease-specific survival advantage. The hope of early detection with annual exams also comes into question given the more advanced stage of the non-small cell lung cancers detected during incidence screening in the Mayo study. The false negative readings with cancer detected on incidence screening retrospectively suggests that spiral CT screening may not yet be ready for routine use. The effect on mortality of the early detection of early stage lung cancer by spiral CT needs to be addressed prior to its widespread adoption into clinical practice. In light of Strauss' reanalysis of the Mayo Lung Project, spiral CT may need to be compared to conventional chest roentgenography to determine the more cost-effective manner of large-scale screening. The National Cancer Institute is currently undertaking such a trial, the National Lung Screening Trial (NSLT), to compare standard yearly chest roentgenography versus yearly spiral CT screening over a 3-year screening period to determine if either offers a benefit in lung-cancer-specific mortality reduction. We would currently advocate that all patients undergoing screening spiral CT for early lung cancer detection have it performed at a center as part of a clinical trial examining its effects on lung-cancer-specific mortality reduction.

Autofluorescence bronchoscopy

Autofluorescence bronchoscopy raised the possibility of detecting early metaplastic and dysplastic lesions as well as carcinoma in-situ. In 1993 the Laser Induced Fluorescence Emission (LIFE) bronchoscopy system (Xillix Technology Inc., Richmond, British Columbia, Canada) was introduced [31]. Early work with the LIFE system demonstrated improved sensitivity for the identification of precancerous and early microinvasive carcinomas. In addition to the LIFE system, the D-Light [32] AF system (Karl Storz Endoscopy America, Culver City, California, USA), Diagnostic Auto-Fluorescence Endoscopy (DAFE) (Richard Wolf Endoskope, Knittlingen, Germany) and the System of Autofluorescence Endoscopy (SAFE 1000©) [33] (Pentex Corporation, Asahi Optical, Tokyo, Japan) have been developed using nonlaser light sources for tissue stimulation. Studies involving the LIFE, D-Light and SAFE 1000 systems have generally been

Table 18.2 Sensitivity and specificity of white light versus autofluorescence bronchoscopy by study.

Author	*AF system*	*Number of patients*	*Known cancer*	*Sensitivity*		*Specificity*	
				WLB	*WLB + AF*	*WLB*	*WLB + AF*
Lam [36]	LIFE	94	Yes	48.4%	72%	94%	94%
Lam [37]	LIFE	173	Yes	WLB + AF 2.71 relative sensitivity versus WLB alone			
Venmans [39]	LIFE	33	Yes	78%	100%	88%	60%
Kakihana [33]	SAFE 1000	72	Yes	66%	92%	54%	56%
Venmans [40]	LIFE	95	Yes	78%	89%	88%	61%
Haubinger [32]	D-Light	60	No	33, 81%*	83, 81%*	94%	89%
Beamis [34]	D-Light	300	Yes	10.6%	65.9%	94.6%	72.7%

WLB, white light bronchoscopy; WLB + AF, white light bronchoscopy followed by autofluorescence bronchoscopy.

*Sensitivity for dysplasia and carcinoma in situ versus tumor.

of small size, and predominantly limited to patients with known or suspected malignancy. Sensitivity of white light bronchoscopy (WLB) has ranged from 10.6 to 85%, compared with a sensitivity of WLB + AF of 72–94% (Table 18.2) [32–40]. In the largest LIFE series, Lam *et al.* reported on the relative sensitivity of LIFE + WLB versus WLB alone [37]. Per patient relative sensitivity for moderate dysplasia or more advanced lesion was 2.0, 6.3 for intraepithelial lesions and 1.46 for invasive carcinoma. A downside of AF is the low specificity versus its high sensitivity for the identification of abnormal tissue, requiring a number of biopsies that would have otherwise not been performed. Lam *et al.* reported 864 biopsies from 173 individuals being examined of which 700 could be evaluated. Another downside is the additional time required to perform AF for screening. Average time for performance of AF + WLB was 23 min, compared with about 9 min for WLB alone [37]. This is longer than the time reported by Pierard *et al.* [41] who performed WLB and both LIFE and SAFE 1000 examination, requiring 23.9 ± 5.4 min on average to perform all three examinations.

The utility of AF as a screening tool in a high-risk but cancer-free population was evaluated in two chemoprevention trials using the LIFE system [42]. The authors concluded that LIFE + WLB did not improve their detection of metaplastic or dysplastic lesions over WLB alone. This data differs from other studies using AF that have demonstrated a greater sensitivity for precancerous lesions with AF than with WLB alone. Outside of the small D-Light study by Haubinger [32], AF bronchoscopy has not been applied as a screening tool for early lung cancer detection in high-risk patient populations without known or suspected lung cancer.

The data from the AF bronchoscopy studies performed unintentionally identify another question in the management of lung cancer patients – what is to be done when dysplasia is identified on biopsy? Bota *et al.* performed serial AF examinations of patients at risk for lung cancer, with subsequent examinations and biopsies determined by the results of abnormal histology [43]. As expected, reserve cell hyperplasia, severe dysplasia and carcinoma in situ lesions were at high risk for progression to invasive neoplasia. The low grade (mild and moderate) dysplastic lesions identified tended to regress or stabilize, with less than 1% progressing to a more aggressive disease. As the majority of biopsies in all series demonstrated mild or moderate dysplasia, this suggests the AF endoscopy may be overly sensitive and require excessive biopsies. Until there is a clearer understanding of the findings of dysplasia, these changes will remain a difficult clinical question. Trials of AF bronchoscopy similar to the ELCAP format are needed to determine the sensitivity of this tool and its effect

on early lung cancer detection and cancer-specific mortality.

Post lung cancer resection screening

Individuals, status-post resection of Stages I and II non-small cell lung cancer are a population at high risk for both recurrent lung cancer as well as for the development of metachronous primary disease. Recurrent disease can often have more limited treatment options than the original primary tumors secondary to previous management. Development of a metachronous lesion often has a broader range of treatment options available [6]. The risk of developing a second lung cancer in patients post resection of non-small cell lung cancer is approximately 1–3% per patient per year and is likely higher in patients who continue to smoke. Approximately half of these patients are able to undergo resection of the second primary tumor [5].

The ACS does not have published guidelines for screening patients after surgical resection of lung cancer. A clinical practice survey of the Society of Thoracic Surgeons regarding follow-up of patients after resection of Stage I non-small cell lung cancer suggested that office visits and serial chest roentgenograms were the primary means of clinical follow-up [10]. A minority advocated the use of chest CT and bronchoscopy. Low-dose spiral CT and AF bronchoscopy were not included in the survey. At this time there is no data on spiral CT for follow-up in this population. AF bronchoscopy has had one small screening trial in the post-resection population. Twenty-five patients (80% Stages I and II) post-resection of non-small cell lung cancer were evaluated. Twelve percent of patients were found to develop intraepithelial or invasive carcinoma postoperatively [44]. Evaluation with LIFE bronchoscopy examination occurred on average 20.5 months after resection. LIFE had an increased sensitivity of 300% over WLB, and identified three of four patients with new airway cancer. No mortality data was presented, nor data suggesting how this information guided subsequent therapy. Larger studies using AF bronchoscopy both preoperatively and as postoperative screening for the development of new primary airway cancer will be needed to determine if this will decrease lung-cancer-specific mortality.

Conclusions

There is no consensus on early screening modalities for patients at risk for lung cancer. Based on studies reviewed we would agree with ACS statement against early screening tests for asymptomatic individuals at risk in clinical practice, but would recommend that individuals interested be encouraged to enroll in clinical trials evaluating these technologies. This recommendation could change with supportive incidence data from repeat annual screening from ongoing studies. However, until there is evidence of reduction in lung-cancer-specific mortality with spiral CT scanning, use outside an investigational protocol cannot be recommended. The NSLT is a large-scale prospective cohort study evaluating for a lung cancer screening specific reduction in mortality, comparing standard chest roentgenography to spiral CT. There is no control group that is not being screened; therefore mortality benefit will have to be inferred from historic controls. Spiral CT screening of patients post resection of early stage lung cancer for the detection of second primary tumors needs to be evaluated, given the potential for improved disease-free survival of patients with early stage lung cancers. AF bronchoscopy is the other screening technology that holds promise, but as a screening tool it remains investigational. Larger trials involving asymptomatic individuals at increased risk of lung cancer will eventually need to be performed to determine the role of spiral CT in screening the population at large. Additionally, the additive effects of spiral CT and AF bronchoscopy could be studied, as they would appear to be complementary in patients at high risk of developing lung cancer.

A recent retrospective review of a patient database examined the correlation of tumor size and survival in patients with Stage IA non-small cell lung cancer [45]. Five hundred and ten patients with Stage IA disease (T1N0M0) were identified over an 18-year period. Cox proportional hazards modeling were used to examine the effect of tumor size on survival. The authors identified no statistically significant relationship between tumor size and survival. This study suggests that the earlier

detection of lung cancer at smaller lesion size versus a larger size may not affect cancer-specific mortality. Van de Vijver *et al.* used microarray analysis of genetic material from a tumor bank of breast carcinoma tissue to discern between a good prognosis or poor prognosis based upon gene expression patterns [46]. The gene expression profile reported by the authors was found to be a better predictor of survival and the development of metastatic disease than the staging systems currently being used. This raises the possibility that tumor gene expression early in the development of the tumor may have more impact on the natural history of the tumor than the stage at which it is diagnosed. This may further help explain why 20–30% of patients with Stage IA lung cancer develop recurrent disease after expected curative resection, and why early detection by currently proposed screening techniques have not demonstrated the mortality benefit that it intuitively should.

The management of patients at risk of lung cancer remains a difficult and vastly unanswerable topic at this time. Screening, as it exists, has not demonstrated clear evidence based data as to the most appropriate approach. Not only does further evidence based research need to be performed, examining the tools we now have available, but good research needs to be performed to further define that population truly at "highest risk" for the development of lung cancer. Even with continued technological development of both radiographic and endoscopic tools, without clearly evaluating which populations to screen it will be very difficult to develop a true broad-based, cost-effective screening program.

Overall, the ideal would be screening patients at high risk, identifying cancers in them early and offering the least invasive yet fully comprehensive treatments possible. Unfortunately it remains only an ideal.

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CHAPTER 19

Staging of bronchogenic carcinoma: an interventional pulmonary perspective

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One of the critical tools that has undergone continued refinement over the past six decades is the staging system that has been developed for lung cancer. Growing out of initial recommendations by Pierre Denoix in 1946 for classifying tumors according to a TNM (tumor, regional lymph mode, metastasis) scheme with subsequent revisions by the International Union Against Cancer and the American Joint Commission on Cancer (AJCC), the importance of the proper clinical and pathological staging of lung cancer cannot be overemphasized [1–5].

The systematic classification of the clinical and pathological staging of lung cancer aids the medical community and patients, not only in the estimation of the anatomical extent of the cancer, but, also, its correlation to survival. Therefore, classifying individual patients into distinct stages has been recognized as the standard for entering patients into clinical trials as well as comparing treatment regimens and prognostic indicators [5].

The clinical staging system is then as outlined in Tables 19.1 and 19.2 by Mountain in his work with the revisions in the International System for Staging Lung Cancer [4]. While this staging schema remains the standard for classifying patients according to the extent of their disease, a modification of this system to allow practical application utilizing the diagnostic tool of bronchoscopy was proposed by Dr. Ko-Pen Wang in 1994 [6,7].

This modification was not meant to replace the International Staging System but, rather, to be utilized as a practical tool in interventional pulmonology to correlate well-recognized bronchoscopic landmarks with common locations of mediastinal adenopathy. This easily usable clinical diagnostic tool is as presented in Tables 19.3 and 19.4 and will be utilized in this work. AJCC stations 1, 2, 3 and 4 are combined as station 3 in this system owing to the fact that stations 1, 2 and 3 in the AJCC system are rarely involved without involvement of station 4. AJCC stations 5 and 6 are able to be sampled only by transthoracic needle aspiration (TTNA) or mediastinotomy and are thus eliminated in this 11-station system [8]. Station 7 is expanded to include the anterior and posterior carina as well as sub- and subsubcarinal lymph nodes as these are considered central mediastinal N2 stations. Only stations 7, 9 and 11 are considered as N1 hilar lymph nodes, which is equivalent to the station 11 interlobar lymph node by the AJCC and American Thoracic Society (ATS) systems. Station 5 and 6, the right and left main bronchus nodes, are considered as N2 mediastinal in our system which are N2 in the ATS system and most recent AJCC system.

Relevant anatomy

The successful use of transbronchial needle aspiration (TBNA) involves not only a thorough understanding of instrumentation, technique and

Table 19.1 TNM (tumor, regional lymph nodes, metastasis) descriptors. Reproduced from [5] with permission.

Primary tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Tis Carcinoma in situ.

T1 Tumor 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus* (i.e. not in the main bronchus).

T2 Tumor with any of the following features of size or extent:

- >3 cm in greatest dimension;
- involves main bronchus, 2 cm distal to the carina;
- invades the visceral pleura;
- associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus <2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with a malignant pleural or pericardial effusion; or with satellite tumor nodule(s) within the ipsilateral primary tumor lobe of the lung.

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor.

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).

N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s).

Distant metastasis (M)

MX Presence of distant metastasis cannot be assessed.

M0 No distant metastasis.

M1 Distant metastasis present.

*The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid show no tumor. In these cases, the fluid is nonbloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a **staging** element and the patient's disease should be staged T1, T2 or T3. Pericardial effusion is classified according to the same rules.

Separate metastatic tumor nodule(s) in the ipsilateral nonprimary tumor lobe(s) of the lung also are classified M1.

preparation of slides for cytology, but also requires the bronchoscopist to have a detailed understanding of the relationship between the tracheobronchial tree and associated mediastinal and vascular structures. To aid the bronchoscopist, four levels in the tracheobronchial tree were selected that are readily identified not only on computed tomography (CT) scan of the chest, but also during endobronchial inspection. These four bronchoscopic levels are the main carina, right upper lobe bronchus, bronchus intermedius and left upper lobe spur. These four levels correspond to eleven nodal stations that are readily and safely sampled by TBNA (Figure 19.1). The eleven nodal stations correspond to those found to be most commonly and consistently involved with metastatic tumor (Figure 19.2) [6,7].

On CT scan the main carina is identified by the change of shape of the trachea to triangular or oval in appearance. At the carinal level there are

six nodal stations: (i) anterior carina, (ii) posterior carina, (iii) right paratracheal, (iv) left paratracheal or aorto-pulmonary (AP) window, (v) right main bronchus and (vi) left main bronchus (Figure 19.3). Anterior carinal lymph nodes are those defined as lymph nodes in front of the main carina. This level often coexists with the visualization of the azygous arch and such a node may be described an "azygous node." To puncture the anterior carinal node the needle is placed in the first or second intercartilagenous space from the lower part of the trachea at about the twelve–one o'clock position (Figure 19.4). Station 2 is the posterior carinal node, which is located posterior to the trachea at the level of the main carina. The CT scan will demonstrate this node often more posterior to the right main bronchus with the puncture site for TBNA being located at the medial posterior wall of the right main bronchus at about the five–six o'clock position. Although no major vessels exist in this area, care should be taken to insure the presence of adenopathy in this region as in the absence of an enlarged lymph node puncture of the azygoesophageal recess may occur possibly producing a pneumothorax. Station 3 defines the right para-tracheal node which is located anterior and lateral to the trachea and posterior-medial to the superior vena cava above the superior border of the azygous arch. To sample this station a puncture should be made at the second tracheal interspace above the carina at the anterior lateral or approximately one o'clock position. Station 4 is the left paratracheal node and is located lateral to the left lower border of the

Table 19.2 TNM (tumor, regional lymph nodes, metastasis) staging* classification. Reproduced from [5] with permission.

Stage	*TNM subset*
0	Carcinoma in situ
IA	T1 N0 M0
IB	T2 N0 M0
IIA	T1 N1 M0
IIB	T2 N1 M0
	T3 N0 M0
IIIA	T3 N1 M0
	T1 N2 M0
	T2 N2 M0
	T3 N2 M0
IIIB	T4 N0 M0 T4 N1 M0
	T4 N2 M0
	T1 N3 M0 T2 N3 M0
	T3 N3 M0 T4 N3 M0
IV	Any T Any N M1

*Staging is not relevant for occult carcinoma, designated TX N0 M0.

Table 19.3 Wang TBNA staging system: location of mediastinum and hilar lymph nodes for TBNA (defined by CT scan). Reproduced from [6] with permission.

	Location
1. Anterior carina	In front and between proximal portion of right and left main bronchi
2. Posterior carina	Behind and between proximal portion of right and left main bronchi, or directly behind right main bronchus
3. Right paratracheal	Behind superior vena cava and in front of anterolateral aspect of lower trachea near azygous arch
4. Left paratracheal (aortic pulmonary window)	Lateral to trachea near tracheobronchial angulation, below aortic arch and above left main pulmonary artery
5. Right main bronchus	In front of right main bronchus
6. Left main bronchus	In front of left main bronchus
7. Right upper hilar	In front and between right upper lobe bronchus and bronchus intermedius
8. Subcarina	Between right and left main bronchi, at or near level of right upper lobe bronchus
9. Right lower hilar	Lateral or in front of bronchus intermedius, at or near level of right middle lobe bronchus
10. Subsubcarina	Between bronchus intermedius and left main bronchus, at or near level of right middle lobe bronchus
11. Left hilar	Between left upper lobe and left lower lobe bronchus

Table 19.4 Wang TBNA staging system: TBNA site for mediastinum and hilar lymph nodes (defined by bronchoscopy). Reproduced from [6] with permission.

	Location
1. Anterior carina	First and second intercartilage interspace from lower trachea at about 12–1 o'clock position
2. Posterior carina	Posterior portion of carina at about 5–6 o'clock position
3. Right paratracheal	Second–fourth intercartilaginous interspace of lower trachea at about 1–2 o'clock position
4. Left paratracheal (aortic pulmonary window)	First or second intercartilaginous interspace from lower trachea at about 9 o'clock position
5. Right main bronchus	First or second intercartilaginous interspace from proximal right main bronchus at about 12 o'clock position
6. Left main bronchus	First or second intercartilaginous interspace from proximal left main bronchus at about 12 o'clock position
7. Right upper hilar	Anterior portion of right upper lobe spur
8. Subcarina	Medial wall of right main bronchus at about 9 o'clock position, proximal to level of right upper lobe orifice
9. Right lower hilar	Lateral or anterior wall of bronchus intermedius at about 3 o'clock position and 12 o'clock position near or at level of right middle lobe orifice
10. Subsubcarina	Medial wall of bronchus intermedius at about 9 o'clock position, proximal to level of right middle lobe orifice
11. Left hilar	Lateral wall of left lower lobe bronchus at about 9 o'clock, at level of superior segment orifice of left lower lobe

trachea and lies below the aortic arch immediately superior to the pulmonary artery causing it also to be termed the AP window lymph node. The AP window lymph node is sampled by placing the needle very close to the tracheal bronchial angulation as horizontal as possible to the trachea at approximately the nine o'clock position (Figure 19.5). Stations 5 and 6 are the right main and left main bronchus nodes, respectively. Station 5, the right main bronchus node, is sampled by placing the needle in the first or second intercartilaginous space from the proximal right main bronchus at about the twelve o'clock position, while the left main bronchus node is sampled in the first or second intercartilaginous space from the proximal left main bronchus at the twelve o'clock position.

The second level identified is where the right main bronchus nears the right upper lobe orifice as seen on CT scan or by endoscopic view which allows visualization of nodal stations 7 (right upper hilar lymph node) and 8 (subcarinal lymph node) (Figure 19.6). On CT scans, the right upper hilar node (station 7) is identified in front of and between the right upper lobe bronchus and the bronchus intermedius while the subcarinal lymph node (station 8) is identified between the right and left main bronchi at or near the level of the right upper lobe bronchus (Figure 19.6b). To sample station 7, the needle is placed in the anterior portion of right upper lobe spur with sampling of station 8 accomplished by placing the needle at the medial wall of the right main bronchus at about the nine o'clock position just proximal to the level of the right upper lobe orifice.

The third level identified is at the level of the bronchus intermedius near the take-off of the right middle lobe orifice. At this level, stations 9 (right lower hilar lymph node) and 10 (subsubcarinal lymph node) are identified (Figure 19.7). The right lower hilar lymph node (station 9) is located on the CT scan as lateral or in front of the bronchus intermedius at or near the level of the right middle lobe bronchus with the subsubcarinal lymph node (station 10) located between the bronchus intermedius and left main bronchus at or near the level of the right middle lobe bronchus. To sample station 9,

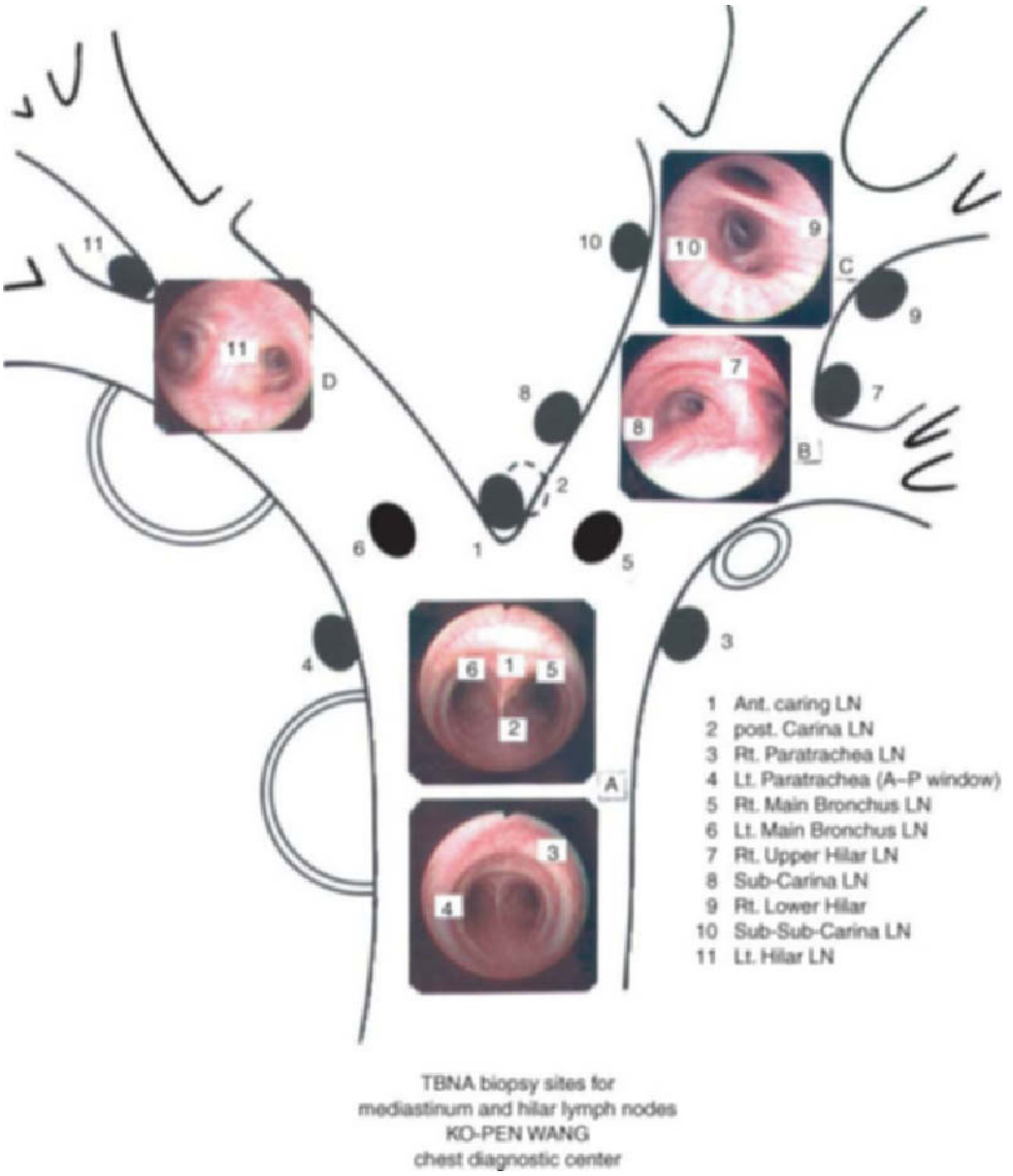

Figure 19.1 Site for transbronchial needle aspiration for mediastinum and hilar lymph nodes (defined by bronchoscopy) Reproduced from [6] with permission.

a puncture should be made at the anterior or lateral wall of the bronchus intermedius at about the three o'clock position and the twelve o'clock position near or at the level of the right middle lobe orifice, with sampling of station 10 performed by inserting the needle at the medial wall of the bronchus intermedius at about the nine o'clock position just proximal to the level of the right middle lobe orifice. The fourth and final level is seen in the left main bronchus at the level of the spur between the left upper and lower lobes (Figure 19.8). On CT scan the left hilar node is identified between the left upper lobe and left lower lobe bronchus and labeled station 11 (Figure 19.9). To sample station 11 a

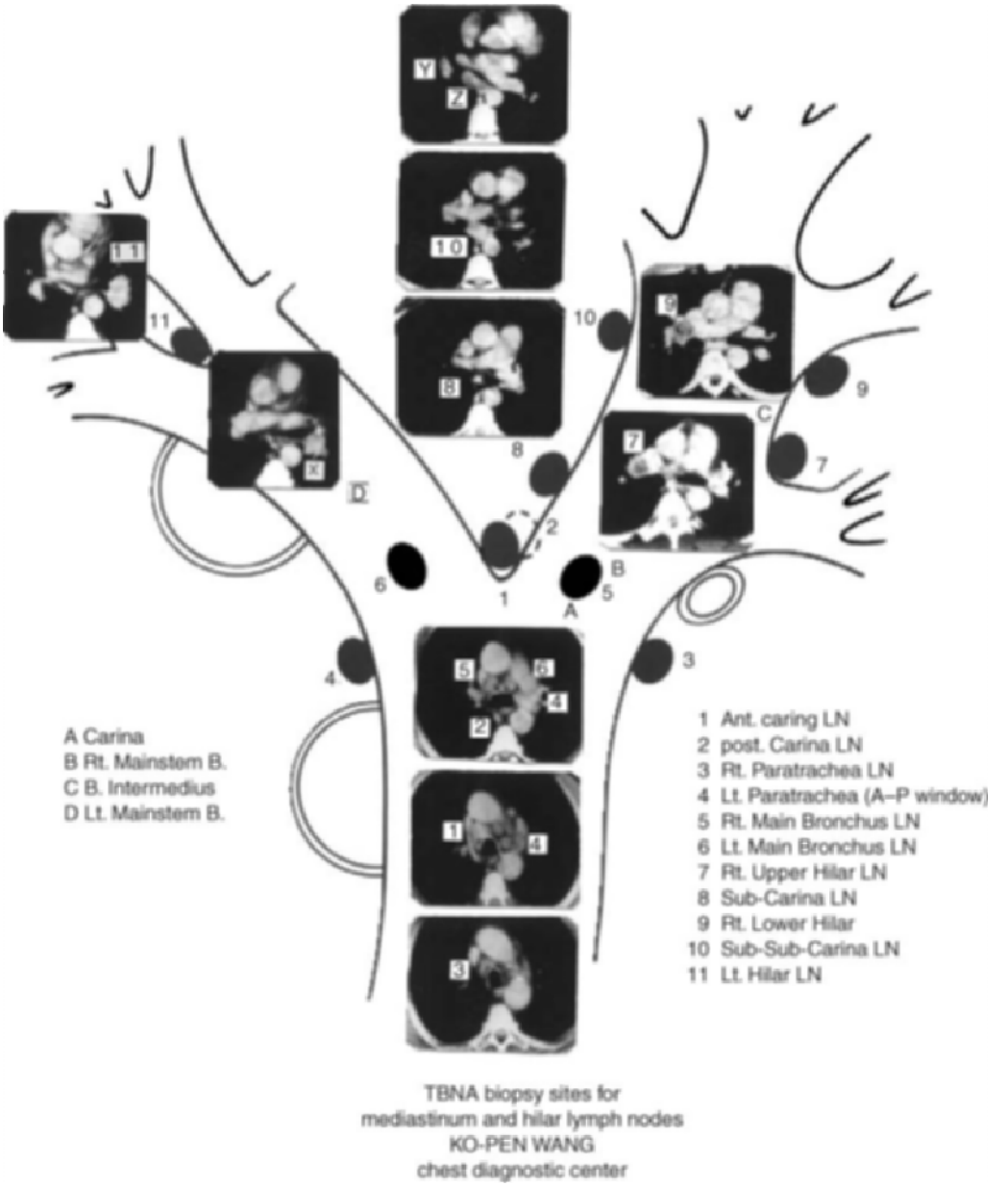

Figure 19.2 Location of mediastinum and hilar lymph nodes for transbronchial needle aspiration (defined by CT scan) Reproduced from [6] with permission.

puncture should be made along the lateral wall of the left lower lobe bronchus at approximately the nine o'clock position at the level of the superior segment orifice of the left lower lobe.

The CT of the chest, then, will provide an anatomic road map identifying involvement of the various stations. It will also be noted that stations 1, 3 and 5, defined as the right mediastinal lymph node chain, are often all involved in metastatic disease and difficult to separate from one another. Also, when sampling the AP window, if the needle is placed too high the aorta may be punctured and

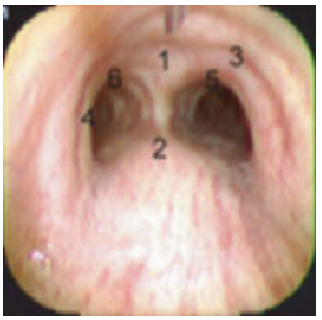

Figure 19.3 Six nodal stations visualized at main carina during bronchoscopy.

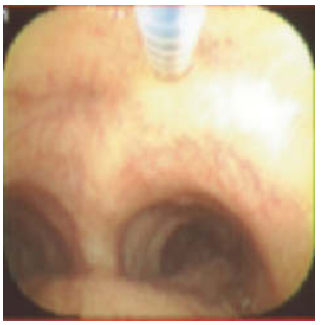

Figure 19.4 Trans brochure needle aspiration at station 1 (anterior carina).

if placed too low the pulmonary artery may be punctured making it important to puncture station 4 as horizontal to the trachea as possible. Puncture of the right upper and lower hilar nodes can be seen to sometimes result in bloody aspiration because of the proximity of the superior pulmonary vein in the case of the right upper hilar node and right main pulmonary artery to the right lower hilar node.

Imaging

A complete discussion of the imaging utilized in the diagnosis and workup of bronchogenic carcinoma is beyond the scope of this case-based chapter; however, there are now several imaging modalities that are regularly utilized in the staging of bronchogenic carcinoma. An initial chest X-ray remains valuable with initial clinical staging inferred from the size of the lesion. Those nodules less than 3 cm and surrounded by lung or visceral pleura being a T1, whereas those more than 3 cm in diameter with atelectasis or obstructive pneumonitis extending to the hilar region being a T2. Initial nodal staging can also be assessed by enlargement of hilar lymph nodes or widening of the mediastinum reflective of mediastinal adenopathy consistent with N2 or N3 disease. The utilization of CT has significantly improved the initial workup of bronchogenic carcinoma, and a CT scan from the apices of the lung caudally to include the liver and adrenal glands is recommended by both the American Thoracic Society and the European Respiratory Society. In determining staging, however, limitations of imaging modalities must be recognized. CT scanning has been demonstrated to have only a 62% sensitivity and a specificity of 84% for detecting invasion of the mediastinum or the chest wall [9].

In an extensive review by Grover, the use of CT in a staging of N2 disease was seen to have a sensitivity of 70–90%, specificity of 60–90% and an accuracy of only 66–90% depending on the definitions used in determining negative or positive adenopathy and subsequent follow-up with surgical staging [10] Another meta-analysis examining the accuracy of CT scan regarding mediastinal adenopathy reported a sensitivity of 79% and a specificity of 78% [11]. Recent data also suggests that size differentiation does not always dictate whether malignancy has invaded local lymph nodes with one review demonstrating 37% of mediastinal lymph nodes 2–4 cm and being hyperplastic but without malignancy [12]. Also in lymph nodes with a transverse diameter of less than 1 cm the possibility of demonstrating nodal metastatic disease still exists in the range of 3–16% [13].

Therefore, some authors conclude that in the staging of lung cancer, the CT scan has a high sensitivity but lacks specificity and that the combination of CT scanning and cytologic or histologic staging allows for the highest sensitivity and specificity to be gained from these techniques [14].

Autoflorescence bronchoscopy

Autofluorescence bronchoscopy has undergone many clinical trials in North America and Europe [15–17]. These trials have involved over 1700 patients and demonstrated that the improvement in rate of detection for dysplasia and carcinoma in situ

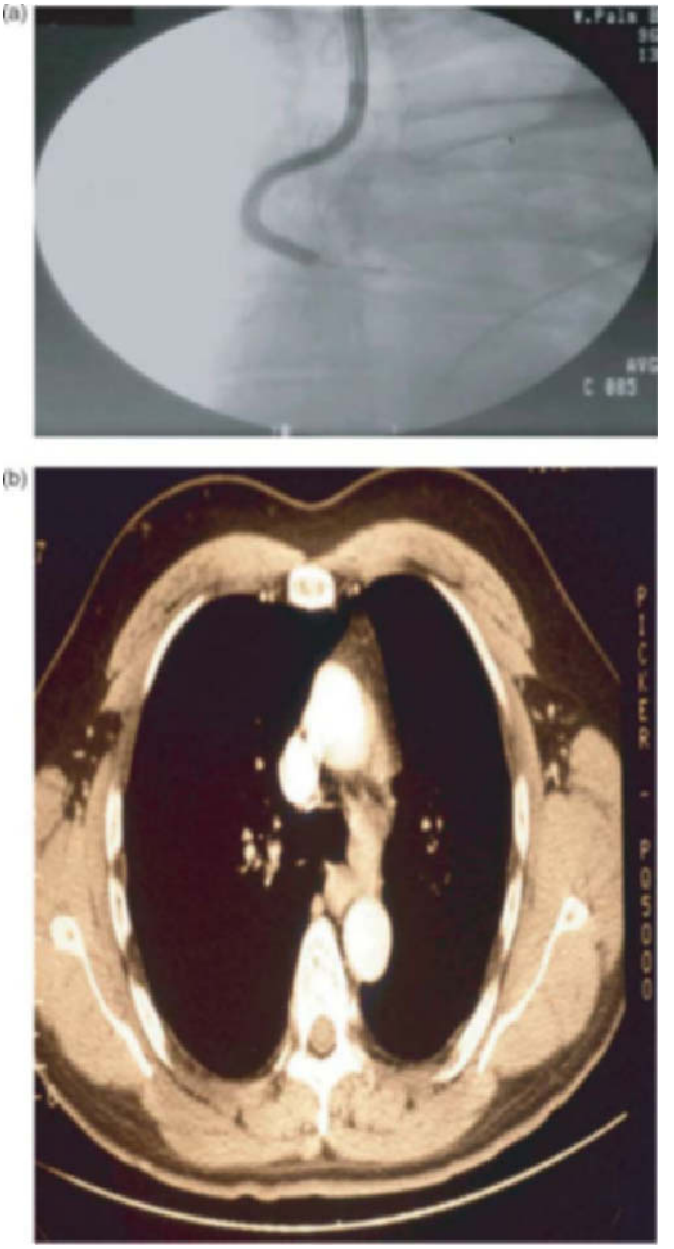

Figure 19.5 (a) Trans brochure needle aspiration at station 4 (AP window). Note angle of insertion between aorta superiorly and pulmonary artery inferiorly. (b) Computed tomography scan demonstrating AP window adenopathy.

was 89 and 128%, respectively. This specificity changed when utilizing white light bronchoscopy from 81% to white light bronchoscopy plus life unit to 60%, with a detection rate increasing from 40 to 80%, respectively. Autofluorescence bronchoscopy works on the basic principle that all tissue fluoresces with appropriate light and emits a unique spectra dependent upon endogenous fluorophores [18] (Figure 19.10). The detection of this unique spectra is then collected by an intensified charged-coupled device (CCD) camera with subsequent image production. The autofluorescent image, then, is seen to be useful in the early detection of mucosal changes of carcinoma in situ and is a valuable adjunct to the

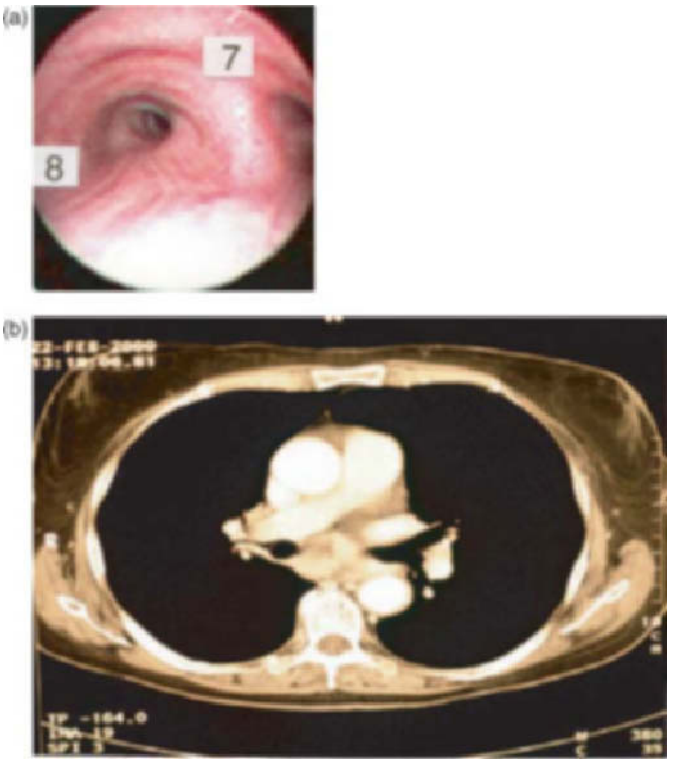

Figure 19.6 (a) Second bronchoscopic level visualizing stations 7 and 8 (right upper hilar and subcarina). (b) Computed tomography scan of subcarinal adenopathy.

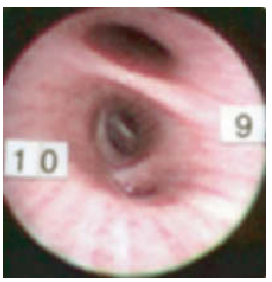

Figure 19.7 Third bronchoscopic level visualizing stations 9 and 10 (right lower hilar and subsubcarina).

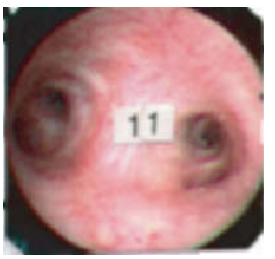

Figure 19.8 Fourth bronchoscopic level visualizing station 11 (left hilar).

early detection of carcinoma with a recent prospective study by Sutedja *et al.* utilizing autofluorescence bronchoscopy to diagnose radiographically occult lung cancer [19].

An additional adjunctive technique in the staging and diagnosis of bronchogenic carcinoma is endobronchial ultrasound. This tool has been utilized over the past decade but continues to be used by few pulmonologists [20]. Widespread acceptance has been hampered by equipment and operator considerations, with initial utilization of 7.5-MHz and 12-MHz probes being hindered by equipment size and low resolution. Subsequently, 20-MHz 2.5-mm diameter probes have allowed the use of endobronchial ultrasound with standard flexible bronchoscopy. Becker and Herth, writing in *Interventional Bronchoscopy*, have outlined the use of endobronchial ultrasound in evaluation of early bronchial carcinoma where they were able to demonstrate deep infiltration of the bronchial

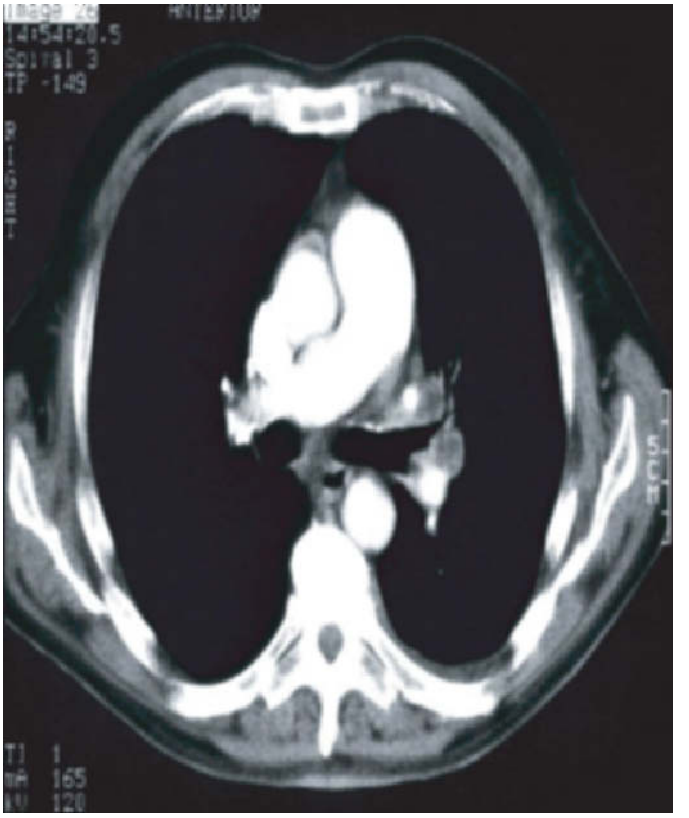

Figure 19.9 Computed tomography scan of left hilar adenopathy.

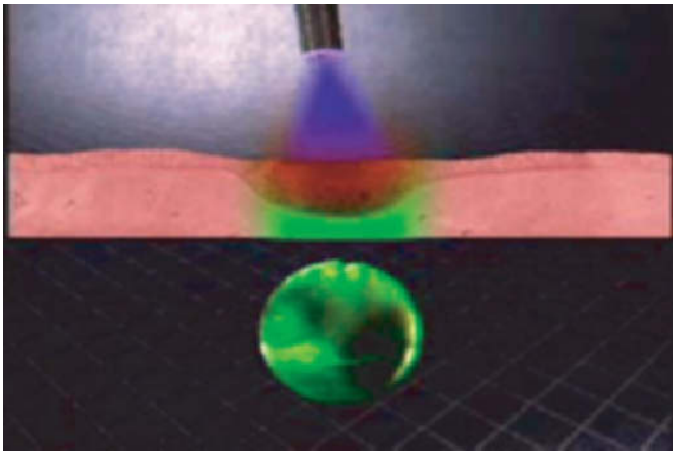

Figure 19.10 Autofluorescence with bronchoscopic image demonstrating carcinoma in situ identified by dark reflection seen at secondary carina. Normal tissue is identified by the green fluorescence seen; From Xillix Website, Xillix LIFE Technology 2002; with permission.

wall in what had previously been felt to be localized carcinoma in situ [19]. Also, ultrasound was utilized in their institution in diagnosing external infiltration of the tracheal wall by tumors of the mediastinal surface of the lung or by primary mediastinal tumors (Figure 19.11). Ultrasound has not only been useful in demonstrating infiltration of adjacent structures but also in the evaluation of lymph node involvement owing to bronchogenic carcinoma. Preliminary results show that

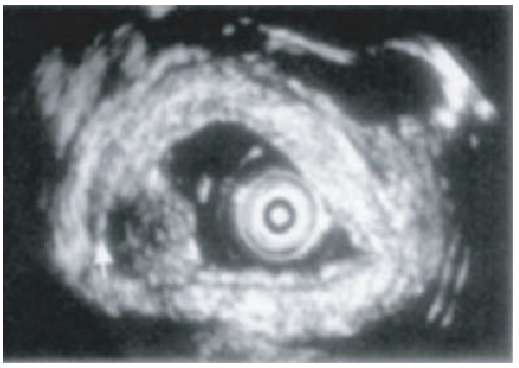

Figure 19.11 An ultrasonogram showing the lesion on the luminal side in contact with the inner marginal echo of the cartilage (white arrow); From Kurimoto N. Assessment of usefulness of endobronchial ultrasonography in determination of depth of tracheobronchial tumor invasion. Chest 1999;115,6:1500; with permission.

prior simultaneous ultrasonography may actually reduce the number of attempts and improve results when performing TBNA for diagnosis and staging [21]. In addition, work from Kurimoto in Japan has shown the utility of endobronchial ultrasound in examining the histopathological correlates of peripheral nodules in the diagnosis of lung cancer [22].

Magnetic resonance imaging may be useful in evaluation of those tumors with close apposition to the diaphragm or the superior sulcus [23]. Nuclear imaging in the staging of lung cancer has seen significant recent improvements. Use of the technetium (Tc) 99m labeled peptide depreotide (NeoTect) is useful in the staging of patients with solitary pulmonary nodules which would be defined as T1 or T2 lesions. The specificity of this test has been quoted to be from 61 to 81% with a sensitivity of 93–99%, a positive predictive value of 87%, and a negative predictive value of 93% [24,25].

Positron emission tomography (PET) scanning with a more widespread clinical utilization has become more readily used in the staging of bronchogenic carcinoma. Utilizing F-fluorodeoxyglucose (FDG), evaluation of lung nodules, nodal disease and distant metastasis is able to be performed with a total body PET scan. Solitary pulmonary nodules have been evaluated with PET scanning with a sensitivity and specificity from 63 to 90%, respectively [26]. Positron emission tomography scanning in the evaluation of nodal disease has been shown to have a sensitivity and specificity of 93 and 99% and a positive predictive value of 90% with a negative predictive value of 93% [27–29]. The utility of PET scanning in metastatic disease has also been found to be a value with 10% of patients found to have metastatic disease not seen on CT with 41% of patients having their management altered owing to information found on FDG PET scanning [30,31].

Patient #1: A 33-year-old woman complaining of a cough.

A 33-year-old white female with a history of breast carcinoma in April of 1999 was referred to the pulmonary clinic by her primary care physician with suspected bronchogenic carcinoma. The patient noted that she had developed bronchitis-like symptoms with a nonproductive cough beginning approximately 2 months prior to being seen. The flu-like symptoms quickly resolved, but she continued to have the cough with worsening dyspnea on exertion. Prior to 2 months ago, she noted she could go out dancing but now became short of breath even walking across the room. The cough worsened with the breathing in of cold air and at night and only relieved with a cough medicine. She denied any hemoptysis, fever, chills or symptoms of rhinorrhea. She denied any symptoms of gastroesophageal reflux. She also noted a pressure-like sensation in her chest, worse with coughing, which was constant.

Her history was remarkable for a stage T2, N0, M0, ER, PR positive breast carcinoma for which she underwent four cycles of Adriamycin and Cytoxan chemotherapy approximately 3 years prior to being seen.

Her examination demonstrated an alert, pleasant woman with stable vital signs. A small, less than 1 cm, freely movable, supraclavicular lymph node on the right was palpable. She had normal heart sounds 1 and 2. Her respiratory exam was remarkable for decreased breath sounds and stony dullness to percussion at the left base. The remainder of her physical examination was unremarkable.

Laboratory studies demonstrated a WBC of 6.3 with a hemoglobin and hematocrit of 12.2 and 35.2 and 388 000 platelets, and a calcium of 10.1. A CT scan of the chest demonstrated narrowing

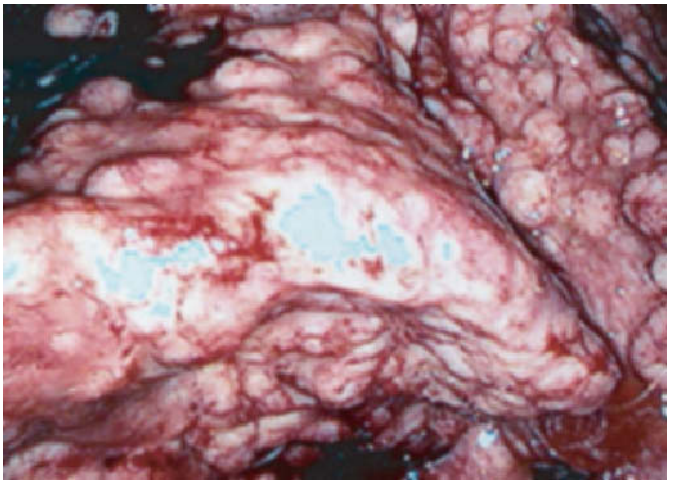

Figure 19.12 Pleural studding of metstatic breast cancer seen at pleuroscopy. (Reproduced with permission from Dr. Kevin Murray.)

of the left lower lobe bronchus and a left pleural effusion. Bronchoscopy was performed with evidence of mucosal polypoid changes and submucosal induration in the distal left main bronchus and left lower lobe. Pleuroscopy was performed for drainage and pleurodesis (Figure 19.12).

Diagnosis: Metastatic breast carcinoma.

Discussion: Patients are often sent to the thoracic endoscopist owing to abnormal imaging studies. In this patient, an abnormal CAT scan raised suspicions of primary bronchogenic carcinoma. With the patient's past history of breast cancer, concern for a recurrence of breast carcinoma with metastasis needed to be considered. Breast carcinoma has a local recurrence rate of approximately 4–20% in the decade subsequent to initial diagnosis [32].

These recurrences are often seen at the chest wall or in the axillary and supraclavicular lymph nodes. Of patients who relapse 50–75% will do so to a single organ, the most common sites being bone, liver, and lung. During the endoscopic procedure, it is important to remember to obtain samples to be sent for receptor analysis such as estrogen receptor, progesterone receptor and HER-2/NEU analysis. This patient demonstrated both estrogen and progesterone receptor positive samples, and she was subsequently referred to medical oncology for evaluation for chemotherapy and endocrine therapy.

Patient #2: A 72-year-old woman with shortness of breath and a lung nodule.

A 72-year-old woman was referred to the pulmonary oncology clinic with a history of shortness of breath. During workup by her primary care physician, a chest X-ray demonstrated a 2-cm nodule in the right lung base with an additional 2-cm well-marginated nodule just anterior to the major fissure in the left upper lung. The patient complained of some dyspnea with activity but felt that she could perform her activities of daily living without difficulty. Although the patient had not smoked for 10 years, she did have greater than 50-pack-year history of smoking. She denied other risk factors for pulmonary nodules such as exposure history, and the only past medical history was an arthroscopy of her left knee.

On examination, her blood pressure was 160/80 with a pulse of 82, with respirations of 19 and temperature of 98.3. Her weight was 210 pounds with a room air oxygen saturation of 97%. Examination of her lungs revealed clear breath sounds bilaterally with the remainder of her physical examination being normal.

Pulmonary function tests were performed which demonstrated an FEV1 of 1.38 l, an FVC of 1.90 l and a DLCO of 57% of predicted.

An echocardiogram was consistent with concentric left ventricular hypertrophy and normal systolic function with a pulmonary artery pressure of 33.

Further workup included bronchoscopy which was normal including a negative examination with

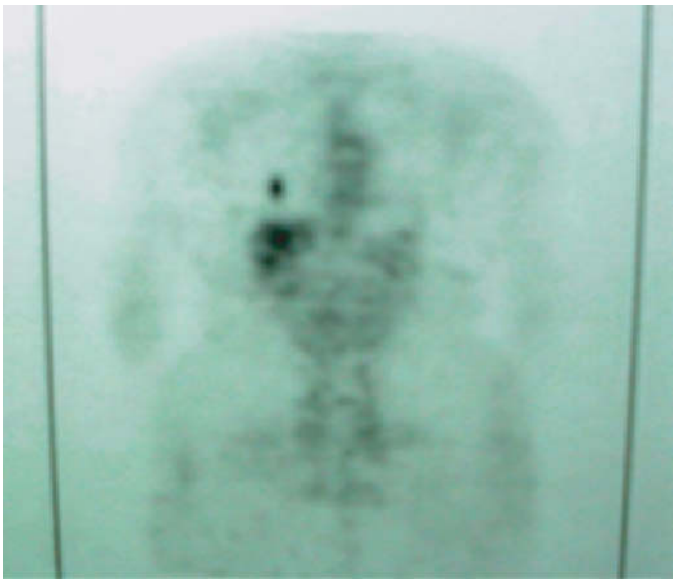

Figure 19.13 Position emission tomography scan demonstrating right lung nodule but no activity at site of left lung nodule.

autofluorescence endoscopy. A PET scan was performed which demonstrated hypermetabolic activity in the right lower lobe nodule with no activity in the left lung nodule which was felt to be old granulomatous disease (Figure 19.13). A quantitative perfusion scan demonstrated only 19% of her perfusion to the right lower lobe. A thoracotomy was performed.

Diagnosis: Adenocarcinoma of the right upper lobe.

Discussion: This patient demonstrates several important principles in the staging and diagnosis of bronchogenic carcinoma. Often the interventional pulmonologist will be faced with patients who initially may be felt to have multiple pulmonary nodules or metastatic bronchogenic carcinoma. As evidenced in this patient, the initial clinical staging may have been consistent with a stage IV bronchogenic carcinoma with a separate nodule in the left lung. With a negative autofluorescence endoscopy to rule out synchronous or metastatic lesions, as well as a PET scan consistent with malignancy in only the right upper lobe, the patient was able to be downstaged to a stage IA. PET scanning has a sensitivity and specificity of 80 and 95% in lesions less than 1.5 cm and 96 and 80%, respectively, in nodules greater than 1.5 cm. Limited resolution in nodules 4–8 mm in size may be the cause of false negatives in small nodules and is thought to be due to partial volume effect with loss of measured activity [33].

Also, preoperative evaluation by the interventional pulmonologist should include careful consideration of the underlying cardiopulmonary status and any comorbid condition. This patient's marked obesity, along with her diminished pulmonary function, were of concern to both the pulmonologist and the cardiothoracic surgeon. Subsequent workup, however, revealed that a right upper lobe lobectomy was possible with predicted postoperative FEV_1 and DLCO of greater than 40% of predicted. The patient underwent right upper lobectomy which she tolerated well and continues follow-up in the pulmonary oncology clinic.

Patient #3: A 54-year-old woman complaining of a sinus infection.

A 54-year-old white female presented to her primary care physician complaining of a sinus infection characterized by productive cough of yellowish sputum and postnasal drip. Her cardiopulmonary review of systems was otherwise only remarkable owing to some self-limited palpitations approximately 1 year prior to being seen. She had a greater than 30-pack-year history of smoking and

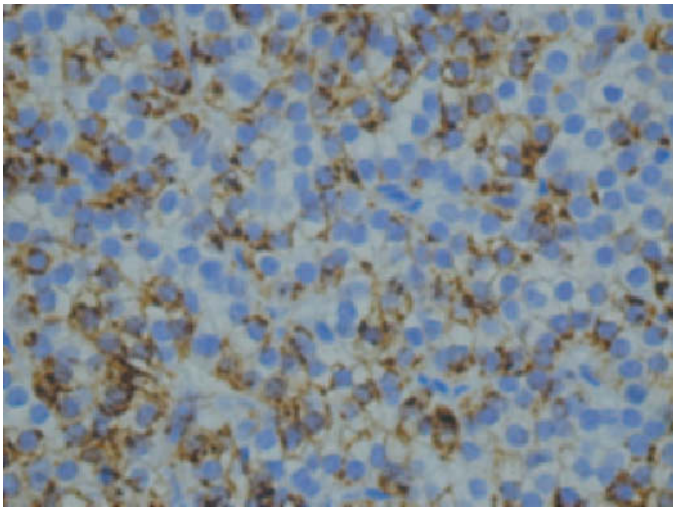

Figure 19.14 Photomicrograph of transbronchial needle cytology demonstrating carcinoid tumour.

stopped 1 week prior to her appointment with her physician. She had no other exposure history.

Past history was remarkable for hypertension, hypercholesterolemia and peptic ulcer disease. The remainder of her history was noncontributory.

Her examination revealed an alert, pleasant lady with a pulse of 100, blood pressure of 112/74 and a respiratory rate of 12. Her physical examination was essentially normal.

Her chest X-ray demonstrated a right paratracheal mass with deviation of the trachea to the left with a subsequent CAT scan showing a 3.3×3.1 smooth-bordered soft-tissue density in the right paratracheal region. An enlarged right lobe of thyroid was also seen, but subsequent workup with a thyroid ultrasound and SPECT scan demonstrated that the thyroid gland was distinct from the mass. Subsequently, the patient underwent fiberoptic bronchoscopy and endobronchial ultrasound. The ultrasound delineated the right paratracheal mass to be without invasion through the cartilaginous layer of the trachea. A transbronchial needle biopsy was performed (Figure 19.14).

Diagnosis: Carcinoid tumor.

Discussion: Carcinoid tumor, one of the neuroendocrine tumors, is rare. Overall, between 1958 and 1998, a report by Hemminki *et al.* demonstrated an age-adjusted incidence range of 2.0 per 100 000 for men and 2.5 per 100 000 for women [34].

Neuroendocrine tumors of the lung such as carcinoid and small cell lung cancer are thought to arise from Kulchitsky cells present in the bronchial mucosa [35].

Most tumors are found to be in a perihilar area. Patients often present with symptoms typical to bronchogenic carcinoma with dyspnea, cough or hemoptysis. Although the tumors are most noted for paraneoplastic syndromes such as acromegaly, carcinoid syndrome or corticosteroid excess (Cushing syndrome), this actually occurs in a minority of patients [36–38].

This patient went on to a complete resection with the surgery demonstrating invasion of the mediastinal pleura but no metastasis to regional lymph nodes (Figure 19.15). She was subsequently felt to have a pathologic T3, N0, M0 tumor stage IIB because of the invasion of the mediastinal pleura but without invasion of any additional structures.

Patient #4: A 57-year-old man complaining of difficulty in breathing.

A 57-year-old Caucasian male was seen in the pulmonary oncology clinic owing to difficulty breathing and an abnormal chest X-ray. He reported to his primary care physician that he had felt well until approximately 3 months prior to being evaluated when he developed scant hemoptysis. He had no complaints of acute illness and denied any fever, chills, wheezing, chest pain or palpitations. The patient's exposure history was remarkable for

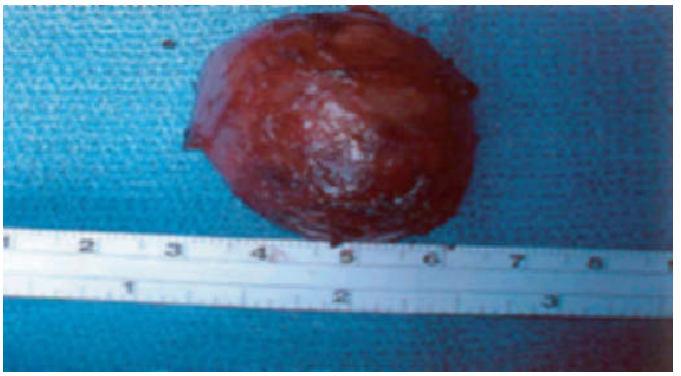

Figure 19.15 Carcinoid tumor removed at time of surgery.

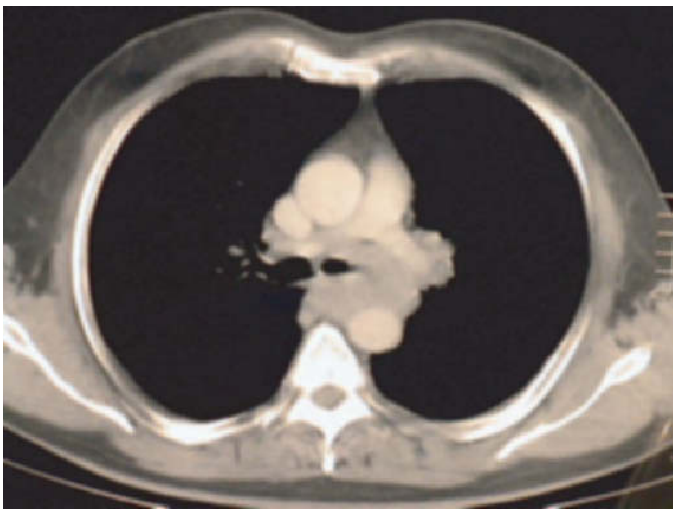

Figure 19.16 Computed tomography scan with mass in subcarinal and AP window (stations 4 and 8).

a greater than 40-pack-year history of smoking. He denied having tuberculosis; however, it was noted that he worked as an aircraft mechanic and lived in an area endemic for coccidioidomycosis. Also of note was the fact that his mother died of lung cancer. His review of systems was remarkable for a 15-pound weight loss and occasional headaches.

His physical examination was essentially unremarkable and his vital signs were normal with a room air saturation of 98%.

Because of the hemoptysis, the primary care physician ordered a chest X-ray which suggested a mass about the left hilus. Subsequent CT scan demonstrated a 5.0-cm × 3.5-cm mass located in the subcarinal region with aortopulmonary window adenopathy (Figure 19.16). A diagnostic procedure was performed.

Bronchoscopy demonstrated significant findings characterized by marked extrinsic compression and abnormal mucosa extending along the length of the left main stem. TBNA was performed in the aortopulmonary window (station 4) which demonstrated small cell carcinoma. Small cell lung cancer, which makes up 15–25% of bronchogenic carcinoma, is characterized by its rapid growth and the development of early distant metastasis. Histologically, small cell lung cancer is differentiated into three types: (i) oat cell, (ii) intermediate cell type and (iii) combined oat cell type [39].

The diagnosis of small-cell carcinoma can be aided with the use of tumor markers with small

cell lung cancer being immunoreactive for keratin, epithelial membrane antigens or neuroendocrine markers such as NSE (neuron specific enolase), synaptophysin, CD57 and sometimes, chromogranin. Additionally, chromosomal analysis has shown that p53 mutations are detected in 90% of small cell lung cancers, but, unlike non-small cell lung cancer, the K-ras oncogene and p16 abnormalities are not seen [40,41].

Staging of small cell lung cancer is distinct from non-small cell lung cancer owing to its rapid growth and propensity for early distant metastasis. A two-stage system developed by the Veterans Affairs lung study group delineates small cell lung cancer into two stages – limited disease and extensive disease. Limited disease is characterized by that which is confined to an ipsilateral hemithorax and being able to be contained within a single radiotherapy port. Extensive disease, therefore, by definition is disease that is metastatic outside the ipsilateral hemithorax or single radiation port.

Diagnosis: The patient presented in this case was felt to have limited stage disease.

Discussion: Of patients seen with small cell lung cancer 30–40% will fall into this stage; however, the majority will have extensive disease at the time of diagnosis. This patient was treated with combined-modality therapy consisting of chemotherapy and radiotherapy. Subsequent follow-up demonstrated a marked decrease in size of the left hilar mediastinal mass, and, currently, the patient's small cell carcinoma has not progressed.

Patient # 5: A 43-year-old man with multiple pulmonary modules.

A 43-year-old Caucasian male with human immunodeficiency virus had relocated from another state and sought follow-up with a primary care physician for continuation of his antiretroviral therapy. During the course of his initial interview, the primary care physician ordered a chest X-ray, which demonstrated multiple pulmonary nodules. A chest CT was obtained without contrast as the patient refused intravenous contrast administration. The CT scan was remarkable for a 2.7-cm mass in the right apex as well as a 2.3-cm mass adjacent to the right hilum and a 2-cm mass in the right lower lobe. The masses were smooth with lobulated margins and without spiculation. The patient was subsequently referred to the pulmonary oncology clinic. Upon interview, the patient reported he was referred only for an abnormal CAT scan and denied any cardiopulmonary complaints. He also denied any additional symptoms upon his review of systems and felt that his health was quite stable on antiretroviral therapy. The patient was noted to be an active smoker with a greater than 30-pack-year history and also had lived in the San Fernando Valley of California until the prior year. A diagnostic procedure was performed.

Diagnosis: Stage IV non-small cell carcinoma.

Discussion: The patient underwent transthoracic needle biopsy without complications. Pathology of the biopsy from the right upper lobe mass demonstrated a poorly differentiated non-small cell carcinoma with squamous cell carcinoma favored. This patient presented with multiple pulmonary nodules and was clinically a stage IV disease. In 1997, Dr. Mountain published revisions of the International System for Staging Lung Cancer wherein satellite tumor nodules within the ipsilateral primary tumor lobe were classified as T4 disease (4). However, those patients with satellite tumor nodules in ipsilateral nonprimary tumor lobes were classified as M1 disease. In this patient, standard chest radiography would have allowed clinical staging of the patient as M1 disease without resorting to a CAT scan once cytologic diagnosis was confirmed. However, the American Thoracic Society and European Respiratory Society recommend that CT scans be obtained in patients being evaluated for non-small cell lung cancer. CT scanning from above the apices of the lungs to the adrenal glands allows evaluation of more distant metastatic disease to include the liver or adrenal glands. Third or fourth generation CT equipment is utilized with slice intervals of less than or equal to 10 mm. This also allows evaluation of mediastinal lymph node metastasis with a sensitivity of 79% and specificity of 78%.

However, "tissue is the issue" remains the standard for pathologic staging of lung cancer owing to the sensitivity and specificity of CT staging for nodal disease. With the increased sensitivity and specificity of PET scanning (95 and 83%,

respectively), additional nodal biopsies may be able to be avoided in the future [42–44].

Patient # 6: A 78-year-old woman with shortness of breath and a left hilar mass.

A 78-year-old white female was referred to the interventional pulmonary clinic owing to a left hilar mass. She had come to her primary care physician and was subsequently referred to a pulmonologist with a history of "bronchitis" with a persistent cough of whitish phlegm. She had noted a gradually worsening shortness of breath in the 6 weeks prior to being seen with an increase in her cough frequency. She denied any hemoptysis, wheezing, chest pain or palpitations. Her exposure history was remarkable for a greater than 50-pack-year history of smoking as well as her mother and brother having carcinoma of an undetermined type. Her past history was remarkable for type 2 diabetes mellitus, hypertension and glaucoma.

On examination, she was alert and in no distress. However, she would become short of breath on moving about the room. She had no supraclavicular or cervical adenopathy. Heart sounds were normal 1 and 2. Respiratory examination demonstrated some scattered rhonchi in the left midlung field but was otherwise clear.

Laboratory findings were unremarkable. However, pulmonary function tests demonstrated an FEV_1/FVC ratio of 44% of predicted with an FEV_1 of 0.75 l and an FVC of 1.69 l, respectively. Her total lung capacity was increased at 117% of predicted and her DLCO was only 50% of predicted. CT scan demonstrated a left hilar mass. CT examination demonstrated a mass in the region of the left lower lobe bronchus. A PET scan was performed which was remarkable for hypermetabolic focus in the left lower lobe bronchus correlating with the abnormal area of density seen on the CT scan (Figure 19.17). Bronchoscopy was performed.

Figure 19.17 Position emission tomography scan with hypermetabolic focus in left hilar area.

Diagnosis: Squamous cell carcinoma obstructing the left main bronchus.

Discussion: This patient demonstrated characteristics, which are very common in patients with primary bronchogenic carcinoma. Approximately 70% of patients are seen owing to new or changing symptoms referable to their underlying carcinoma. Forty-five to seventy-five percent of patients present with the nonspecific symptom of cough or a change in the characteristic of the chronic cough they have attributed to underlying lung disease [45].

Upon bronchoscopy, this patient was found to have an obstructing polypoid mass of the left lower lobe (Figure 19.18). This patient due to the obstructing lesion of a main bronchus 2 cm distal to the main carina with the PET scan demonstrating no additional intrathoracic or extrathoracic uptake is consistent with a T2, N0, M0 upon clinical staging and, thus, represents a stage IB bronchogenic carcinoma. Subsequently, the patient underwent laser photoablation with opening of the left lower lobe bronchus to the subsegmental region. She was discharged to her primary pulmonologist with consideration for adjuvant chemotherapy with an epidermal growth factor receptor inhibitor.

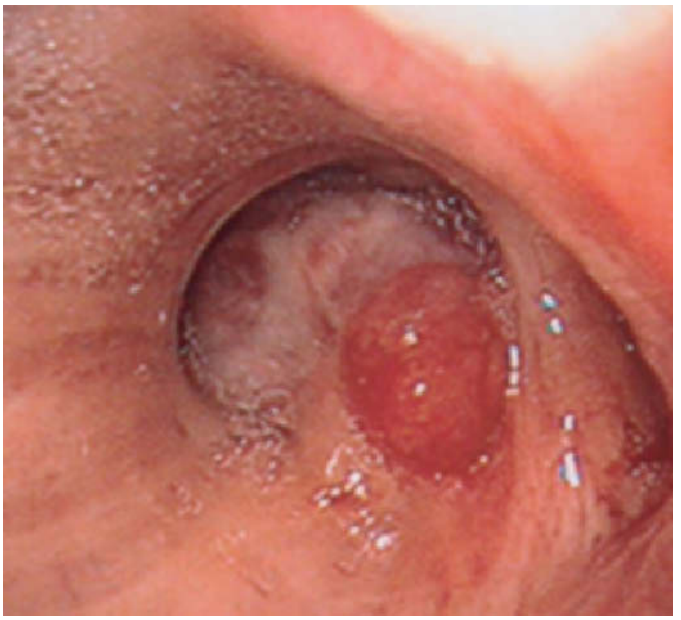

Figure 19.18 Obstructing mass of left lower lobe.

Acknowledgment

The authors wish to acknowledge Dr. Ko-Pen Wang for the use of figures, photographs and for his continued inspiration.

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20 CHAPTER 20

Management of malignant pleural effusions

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Introduction

Malignant pleural effusions (MPEs) are an increasingly important medical issue encountered by a wide range of clinicians, including general practitioners, pulmonologists, surgeons and oncologists. MPEs develop in many advanced malignancies, and often produce debilitating symptoms such as dyspnea and chest discomfort. In one study from Spain, 15% of patients who died with a malignancy were found to have a malignant effusion [1]. Non-small cell lung cancer accounts for over one-third of MPEs, followed by breast cancer lymphoma, mesothelioma, ovarian cancer and gastric and esophageal cancer [2–4]. Pleural effusions can arise as a direct consequence of neoplastic invasion of the pleural space ("true" malignant effusions) or as an indirect result of the underlying cancer (para-malignant effusions). "Para-malignant" effusions develop as a result of several different factors: post-obstructive atelectasis, trapped lung, pulmonary embolism and compression of lymphatic channels by enlarged mediastinal lymph nodes. This chapter will focus on the management of true MPEs using guidance from recent literature as well as our own clinical experience at the Hospital of the University of Pennsylvania.

There are many variables one must account for when treating a patient with a symptomatic MPE. Underlying disease, life expectancy, cost, length of hospital stay, patient preference and physician experience all play a role in determining the optimal treatment plan. In general, MPEs portend a poor overall prognosis with a mean survival time of about 6 months [5]. Therefore, an appropriate therapeutic goal in patients with MPEs would be to provide palliative relief of debilitating respiratory symptoms. The aim of the management of MPE is the selection of optimal treatment for patients with limited life expectancy, disabling symptoms as dyspnea and poor general condition. Therefore efforts to palliate symptoms, optimize function, shorten hospitalization and reduce end-of-life medical care costs are required.

Thoracentesis/pleurocentesis

Although a variety of procedures are available for the diagnosis and management of MPEs, the initial procedure of choice remains thoracentesis (or pleurocentesis). Although this procedure is often necessary for establishment of the etiology of the effusion, thoracentesis alone is generally insufficient for the definitive treatment of MPE due to the rapidity of fluid reaccumulation. In fact, one study reported symptomatic fluid reaccumulation within 4.2 days of initial therapeutic thoracentesis [6]. Therefore, except for the most debilitated patients with an extremely short life expectancy, serial thoracentesis is not a practical option for long-term control of MPE.

Effective palliative therapy for symptomatic MPEs necessitates not only the removal of pleural

fluid, but also the induction of an "effective" sclerosis of the pleural space to prevent reaccumulation. The American Thoracic Society (ATS) defines "complete" or effective pleural sclerosis as "long-term relief of symptoms related to a pleural effusion, with absence of fluid reaccumulation on chest radiographs until death" [7].

Current American Thoracic Society consensus guidelines for MPE suggest an initial thoracentesis to establish a diagnosis, followed by standard chest tube drainage with subsequent talc slurry instillation [7]. This approach necessitates an approximate 4–5 day inpatient hospitalization, and can be associated with significant pain, limited mobility and separation from the home environment. Although this approach is quite effective in treating MPEs [8–10], inpatient hospitalization is costly and can be distressing for patients and their families who have probably already experienced multiple hospitalizations related to their underlying malignancy.

Chemical pleurodesis

Patients with MPE failing conservative medical management have traditionally been referred for chemical sclerosis ("pleurodesis") of the pleural space via tube thoracostomy or video-assisted thoracoscopic surgery (VATS). The most common procedure for the induction of pleural sclerosis in MPE involves large-bore thoracostomy tube drainage followed by chemical pleurodesis with various agents such as talc, bleomycin, quinacrine or doxycycline, typically performed in an inpatient setting [3,5,8].

Despite the lack of well-controlled studies of the efficacy of specific chemical irritants in the literature, talc is considered by many clinicians to be superior to other sclerosing agents, with a greater than 90% success rate for talc pleurodesis in the treatment of recurrent pleural effusions [11]. Talc is an inexpensive and highly effective sclerosing agent when administered intrapleurally for pleurodesis. Fever and pain are the most common short-term adverse effects. Pain can be well controlled with the use of intravenous opiates and intrapleural lidocaine (3–4 mg/kg) administered 10–15 min prior to talc instillation [12]. The primary controversy surrounding the use of talc for pleurodesis relates to reports of talc-induced acute respiratory distress syndrome (ARDS) after intrapleural instillation or insufflation [13,14]. Currently, it is not entirely clear if the method of administration (slurry versus poudrage) plays a major role in the development of respiratory failure, or whether the dose of talc (>5–6 g) or preexistent bronchopleural fistulae (i.e. after pneumothorax) are paramount. Most recent publications have emphasized the importance of the size and quality (and geographic origin) of talc particles for the ultimate safety of intrapleural delivery [15–17].

Talc slurry

Talc slurry, an admixture of asbestos-free talc powder and sterile saline in suspension, has been widely utilized for instillation into the pleural cavity for palliative treatment of MPE. The primary rationale for use of talc slurry pleurodesis in the treatment of MPE is the simplicity of this "blind" bedside technique [18]. Systematic evaluation of the efficacy of talc slurry for pleurodesis is impeded by imprecise definition and/or documentation of the specifics of the slurry preparation and technique. In particular, there is no standardization of saline volume, talc dosage, chest tube size, duration of chest tube clamping, insistence on patient rotation, level of wall suction or parameters for chest tube removal.

There are, however, several limitations and problems of talc slurry administration for MPE, particularly in comparison to thoracoscopic talc poudrage (see later). For example, in contradistinction to talc poudrage, chest tube instillation does not result in even distribution of talc particles over the pleural surfaces. With talc slurry instillation, the majority of the talc particles are actually evacuated through the chest tube with the saline solution after reconnection to wall suction. Experimental studies also demonstrate that with talc slurry instillation, pleural inflammation and fibrosis occur mostly in gravity-dependant regions of the hemithorax. As a result, far fewer pulmonary-to-costal adhesions are seen in comparison thoracoscopic talc poudrage [18–20].

In general, talc meets the criteria for an "ideal" pleurodesis agent: high efficacy, ease of administration, low cost and rare severe adverse effects [21]. There are, however, many factors which determine the cost-effectiveness of a sclerosing agent for

MPEs, including necessity and length of hospital stay, personnel costs, costs of diagnostic testing as well as the occurrence and associated costs of adverse effects. Procedural costs remain major contributors to the cost-effectiveness of any approach for management of MPE. Despite talc's low cost and high efficacy, sophisticated procedures required for talc delivery, i.e. medical thoracoscopy may diminish the cost-effectiveness of the overall management approach [18,22].

In an attempt to reduce these costs, ambulatory management of MPE with talc slurry pleurodesis has been performed via small-bore pleural catheters (PCs) [23]. The feasibility of this outpatient procedure has been demonstrated in relatively small numbers of patients, but with reported 30-day response rates similar to those reported for inpatient talc slurry pleurodesis, and consequently with a potentially lower associated cost. The need for expensive outpatient supplies, however, may increase the overall cost of the procedure, and thereby dampen enthusiasm for outpatient pleural sclerosis [18,24].

The major drawback in the evaluation of inpatient versus outpatient talc slurry pleurodesis is the lack of adequate assessment of efficacy, as reported trials have evaluated small numbers of patients, employed different techniques, used conflicting success criteria and/or monitored subjects for varying periods of time. Moreover progression of disease is variable and the precise nature of intrapleural anatomy of the patients at the time of pleurodesis, i.e. degree of visceral and parietal pleural involvement with malignancy, is unknown [18]. In theory, these biases would be mitigated in well-designed, large, randomized multicenter clinical trials, although these can be quite difficult to implement.

Small-bore catheter drainage

As mentioned earlier, small-caliber chest tube insertion is an increasingly popular therapeutic option that the interventional pulmonologist can offer for management of symptomatic MPEs. These chest tubes can be equipped with one-way valves (i.e. Pleurx catheter®, see later), which facilitates drainage of the malignant effusion on an outpatient basis. A distinct advantage that PCs have over standard chest tube drainage with chemical pleurodesis relates to the decreased morbidity to patients who often have experienced extensive surgical and medical therapy for their primary malignancy. Physician intervention can thereby be minimized and valuable out-of-hospital time preserved during a patient's final weeks or months of life. In addition, as previously mentioned, small-bore catheters can be utilized for achievement of chemical sclerosis of MPEs on an inpatient or outpatient basis [23,24].

Several case series have reported the successful use of small-bore PCs for outpatient drainage and sclerosis of MPEs [25–29]. Several studies have demonstrated that PCs are as effective as standard chest tubes when used for chemical pleurodesis with significantly less pain, cost and hospitalization [30–35]. These early descriptions contributed to the development of a small-bore, flexible, tunneled PC (Pleurx®, Denver Biomedical, Golden, CO, USA) that allows for periodic home drainage of MPEs. These catheters have significantly altered the nature of MPE management as they can be inserted on an outpatient basis with minimal post-procedure discomfort, thereby obviating the need for hospitalization. Furthermore, patients can drain the MPE at home on a scheduled or symptomatic basis, preventing fluid reaccumulation, and potentially achieving pleurodesis without significant pain or hospitalization.

Pleurx® pleural catheter

The Pleurx® PC (Denver Biomedical, Golden, CO, USA) is a 66-cm long, 15.5-F silicone catheter with distal fenestrations. (See Chapter 14) A valve at the proximal end of the catheter prevents fluid or air from entering or exiting the catheter until accession by a unique drainage line. A polyester subcutaneous cuff helps to secure the catheter in place, and thereby minimizes the risk of chest wall or intrapleural infection. After placement, pleural fluid may be drained periodically from the chest into vacuum bottles by connecting the drainage line access tip to the valve [36].

Pleurx® catheter placement is typically performed as an outpatient procedure under local anesthesia, with optional use of conscious sedation. Patients' vital signs and oxyhemoglobin saturation

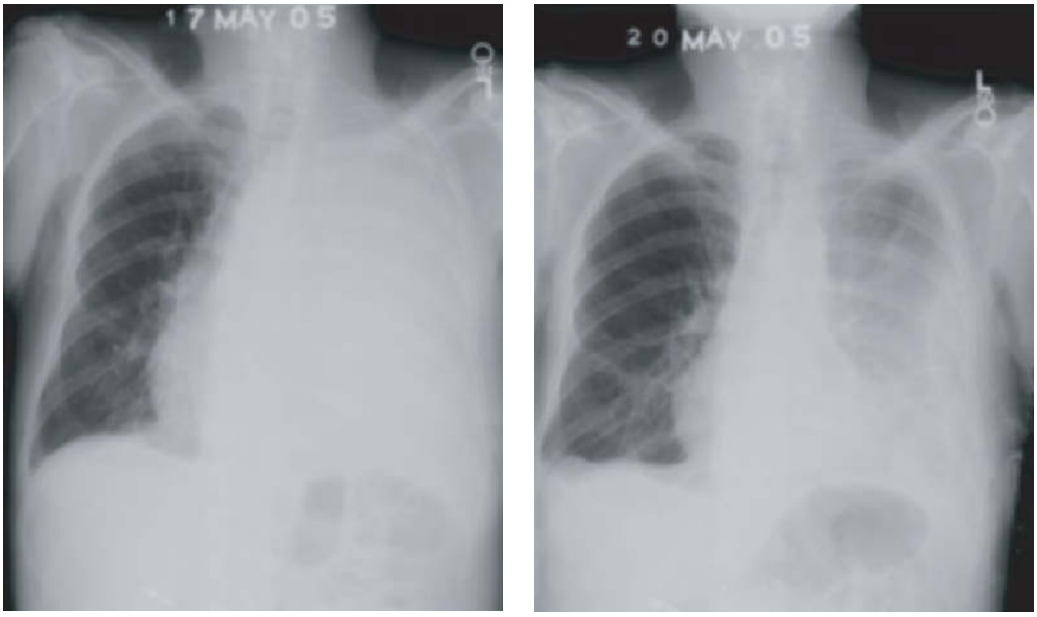

Figure 20.1 Outpatient management of malignant pleural effusion with tunneled pleural catheter. (a) seventy-eight-year old male with malignant pleural mesothelioma of the left hemithorax with recurrent massive left-sided pleural effusion with contralateral shift of mediastinum and trachea. (b) PA chest radiograph 3 days status post left Pleurx® catheter insertion and drainage of over 3 l of serosanguinous pleural fluid. The patient rapidly achieved near-complete relief of dyspnea and chest discomfort.

are continuously monitored throughout the procedure. The catheter is placed using a modified Seldinger technique in the mid-axillary line, as previously described [36], and tunneled under the skin along the lateral chest wall. Alternatively, the PC can be placed via a standard chest tube insertion technique, primarily in partially loculated pleural spaces. After catheter insertion, 1000–1500 mL of pleural fluid is drained immediately and a chest radiograph obtained to evaluate catheter position and assess for the presence of "trapped" lung (Figure 20.1). The catheter can also be connected to a monometer to confirm this diagnosis [37]. Pain medications are prescribed as needed, although the use of oral narcotics for chest wall discomfort beyond 24–48 h after catheter insertion is uncommon. Home pleural drainage of up to 1000 mL per session is performed with the assistance of a visiting nurse or specially trained family members. Patients are evaluated in follow-up for improvement in respiratory symptoms and pleural effusion on chest radiographs (Figure 20.1), and for complications of the PC placement [36].

Our institution has managed over 250 MPE patients over the past 5 years as outpatients, utilizing indwelling PCs such as the Pleurx®. In our experience, the majority of patients with symptomatic MPEs undergoing Pleurx® placement achieved complete or partial pleural symphysis, allowing PC removal, within 2–6 weeks from catheter insertion, without the need for a sclerosing agent. Regardless of whether patients with MPE ultimately attained complete pleural symphysis, nearly all achieved relief of respiratory symptoms [29]. The success rate and/or the rapidity of pleurodesis engendered by Pleurx® insertion can be ameliorated by adjunctive use of a chemical sclerosant such as doxycycline or bleomycin. (Figure 20.2).

There are several hypothetical pathways for the development of pleural symphysis in the absence of use of chemical or physical irritants. These mechanisms are primarily based on the concept that physical separation of the visceral and parietal pleural surfaces by the fluid layer of an MPE is inhibitory to the process of pleural adhesion.

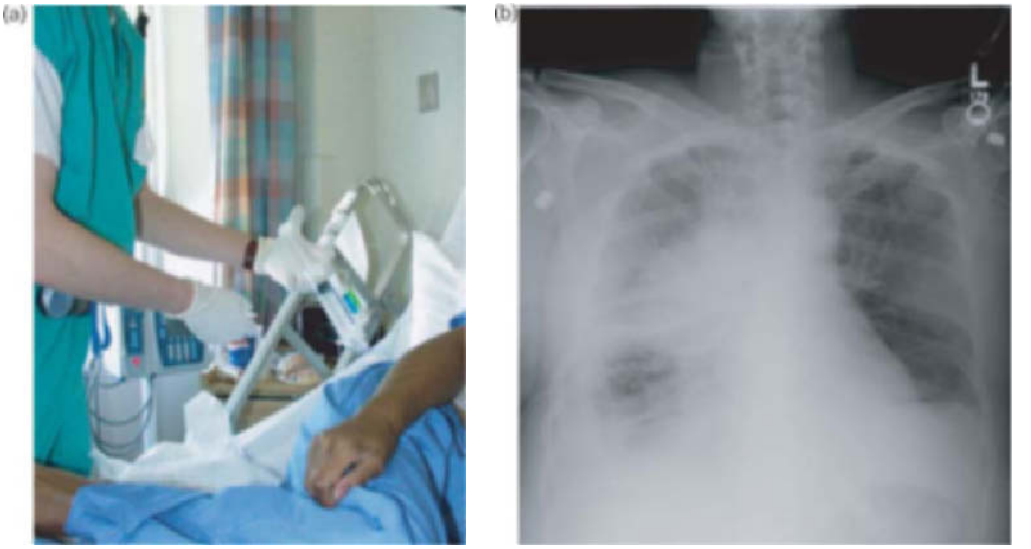

Figure 20.2 Small chest tube mediated chemical pleurodesis. (a) Technique of bleomycin infusion via right pleural catheter in 59-year-old female with refactory malignant pleural effusion secondary to metastatic breast carcinoma with large right mid-lung field mass. (b) Posteroanterior chest radiograph status post successful bleomycin pleurodesis with small thoracostomy tube visible at right base.

Frequent outpatient drainage of the MPE may permit sufficient apposition of the visceral and parietal pleurae to facilitate pleural symphysis. In addition, frequent drainage of the MPE may remove protein, cellular debris or other factors within the MPE that interfere with the process of pleural inflammation. Certain inflammatory mediators (IL-2, TNF-α, TGF-β) released by the pleural surfaces or tumor cells may serve as endogenous sclerosing agents only in the presence of visceral and parietal pleura apposition. Finally, the PC itself may act as a physical irritant to stimulate intrapleural inflammatory responses and fibrinogenesis.

Combining the benefits of a PC previously described with the use of sclerosing agents has broadened the use of PC in MPEs. Talc slurry, however, is a thick mixture which does not flow well through a small-bore chest tube. If incompletely evacuated after instillation and desired dwell time (as can occur with small-bore catheters), attempted talc slurry pleurodesis can result in the formation of multiloculated MPEs. Doxycycline and bleomycin are two agents well suited for use with small-bore catheters. Bleomycin has recently become our preferred mode of chemical pleurodesis through a tunneled PC. A recent Italian study supported the use of intrapleural bleomycin at a dose of 0.75mg/kg (single or repeated dosing) instilled via a small-bore chest tube with a resultant pleurodesis rate of 84% [38]. While this figure may be slightly inferior to the success rate of talc poudrage, combining the outpatient benefits of a Pleurx® catheter makes this an attractive option. The toxicities of intrapleural bleomycin infusion are generally well tolerated, and include fever, tachycardia and mild chest discomfort (Figure 20.2). The cost of bleomycin is substantially more than talc, but the decreased expense of outpatient administration compared to a 4–5 day hospital stay may make the treatments equivalent with the added benefit of outpatient convenience.

Complications related to PC insertion

The complications related to the placement and maintenance of the catheters are generally infrequent. Adverse events occurring during PC placement are unusual, but include bleeding, pain and pneumothorax. The most common post-procedure complications after PC placement are cellulitis localized to the tunnel/insertion site, bacterial infection of the pleural space, development of intrapleural loculations and peri-incisional tumor

growth (particularly with mesotheliomas). In general, these complications can be managed conservatively with antibiotics, PC removal, insertion of a standard thoracostomy tube or palliative radiation therapy [29]. These post-procedural complications are not substantially different from those seen with standard chest tube drainage and talc slurry instillation.

Although MPEs can contain a significant amount of protein, there have been no published reports of protein malnutrition during the period of repeated pleural fluid drainage. This complication could be envisioned if pleurodesis was not attained and large volume daily drainage was required over an extended period. This proved not to be a significant problem in patients with lung entrapped by malignancy [36]. Furthermore, in our experience, reexpansion pulmonary edema is uncommon with PC insertion, as the quantity of fluid drained could be tightly regulated, unlike the situation often encountered with placement of standard chest tubes due to the technical aspects of a larger portal of entry and rapidity of tube placement.

Management of loculated MPEs

Noninfectious intrapleural loculations can be managed successfully with trans-catheter instillation of fibrinolytic agents. In the presence of frank empyema, however, a loculated MPE may be best managed by VATS lysis of adhesions and drainage or even open surgical decortication [39]. Chest computed tomography or ultrasonography should be performed in all patients with MPE prior to placement of the chest tube or PC to evaluate for the presence of loculations, especially if there is a history of previous pleural intervention. Some loculations can be physically disrupted by the individual performing tube thoracostomy (particularly with standard chest tube insertion) using the chest tube itself or a probing finger in the pleural cavity. Additionally, intrapleural loculations can be lysed effectively with insertion of a thoracoscope.

At our institution, we have recently altered our algorithm for dealing with loculated pleural spaces based on our experience with intrapleural instillation of a variety of fibrinolytic agents. Our approach (based on recommendations from two studies published only in abstract form [40,41]), involves instillation of 10 mg of tissue plasminogen activator (or alternatively 250 000 IU of streptokinase) admixed with 50 cc of saline followed by a 20 cc flush of saline through the PC. The patient is then capped and rotated at 15-min intervals for a period of 2 h followed by vacuum drainage. This is repeated two–three times a day for a maximum of 3 days. In several cases of multiloculated MPE, we have consulted our colleagues in interventional radiology for image-guided placement of intrapleural pigtail catheters. These patients were deemed unsuitable for bedside tube thoracostomy or PC insertion due to the location and number of their loculations or a prior history of failure of chest tube drainage. Fortunately, many MPEs are not loculated and often only become loculated after a failed attempt at chemical or physical pleurodesis. In this manner, although PC-directed pleurodesis may take longer to occur, the incidence of loculated effusions may be reduced compared to that of other methods.

Pleuroscopic talc poudrage

The primary treatment modality for many interventional pulmonologists in dealing with patients with recurrent, symptomatic MPE is talc poudrage pleurodesis via pleuroscopy, also known as "medical" thoracoscopy. Pleuroscopy was first described by a European internist named Jacobeus in the early 1900s for use in the diagnosis and management of tuberculous lung disease, specifically for the induction of "therapeutic pneumothorax." Jacobeus' procedure was subsequently abandoned once effective anti-tuberculous medicine became widely available [42,43]. In modern times, the development of video-assisted laparoscopic surgery brought with it a resurgence of interest in pleuroscopy, as well as the advent of VATS techniques [44].

Pleuroscopy differs substantially from VATS in several respects: the focus on diagnosis and palliation; the utilization of conscious sedation rather than general anesthesia; and the use of a single access port rather than multiple incisions. Pleuroscopy can be performed on an outpatient basis in the endoscopy unit and is among the safest procedures at the interventional pulmonologist's disposal. After establishment of port access, air enters the pleural cavity passively, engendering equilibrium in

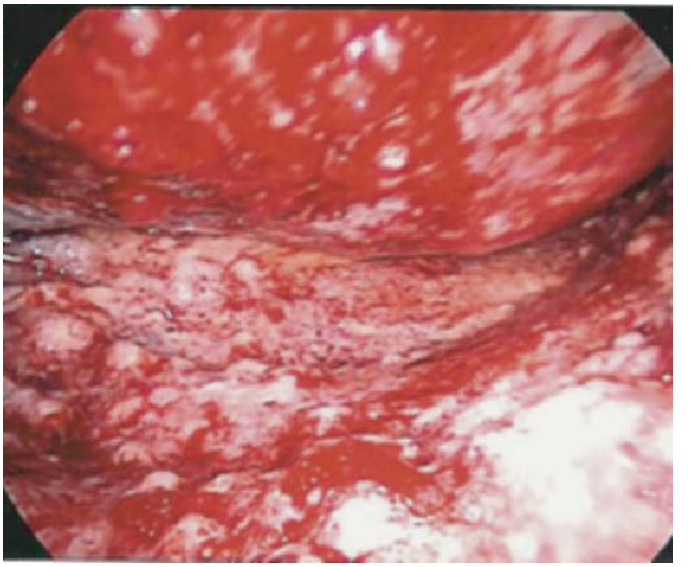

Figure 20.3 Pleuroscopy in malignant effusion. Videothoracoscopic image obtained with Wolf rigid pleuroscope demonstrating diffuse visceral and parietal pleural nodularity and inflammation characteristic of malignant pleural mesothelioma. Directed talc poudrage sclerosis was successfully performed via the pleuroscope after biopses were obtained to establish the pathological diagnosis. (Video image reproduced with permission from William Krimsky, Director, Interventional Pulmonology Program, Sinai Hospital, Baltimore, Maryland, USA.)

extra- and intra-pleural pressures. Complete collapse of the lung allows an excellent view of the pleural cavity and a careful analysis of visceral and parietal pleurae, the opportunity to biopsy suspicious lesions and at the end of the procedure permits a wide distribution of the talc on a dry tissue. Pleuroscopy offers a minimally invasive "window to the pleural space" capable of providing crucial information regarding a variety of pleural pathologies [45].

Appropriately, pleuroscopy plays an important role in the diagnosis and management of MPEs (Figure 20.3). In combination, serial thoracentesis and closed needle pleural biopsy offer at best a 60–80% chance of arriving at a diagnosis of a suspected malignant effusion, whereas thoracoscopic pleural biopsy succeeds in establishing the diagnosis in over 90% of cases. In addition, thoracoscopic talc poudrage provides effective pleurodesis in up to 80–100% of patients with MPE [43]. Pleuroscopy-mediated pleural sclerosis, typically via talc insufflation (poudrage), necessitates a short inpatient hospital stay and is associated with minimal side effects, fever being the most common. In the case of pleuroscopic talc poudrage for MPE, fever occurs in as many as 20–30% of patients [42]. Thoracoscopic guided pleurodesis may be ineffective in patients with bulky pleural disease, trapped lung, long standing effusions or a large obstructing endobronchial mass. Patients with complex, loculated malignant effusions may benefit from traditional VATS or formal open surgical decortication [46], if they have an adequate performance status and expected survival of greater than a few months.

Thoracoscopy's safety record is well established. Peri-operative death rates are extremely low, approximating 0.24% in one study. Complications reported in the literature include bleeding, persistent bronchopleural fistulae and intercostal nerve or vessel injury [45].

Talc poudrage

Pleuroscopic talc poudrage to obtain symphysis in patients with MPE can be performed under general anesthesia or under local anesthesia with conscious sedation. Commonly the procedure is performed with maintenance of spontaneous respiration [47]. Several technical details should be taken into account in order to achieve good pleurodesis and avoid complications: (a) all pleural fluid should be removed before talc insufflation – fluid removal is easily done under visual control during thoracoscopy; (b) use of less than 5 g of sterile, asbestos-free, calibrated talc is recommended to minimize risk of respiratory complications without compromising efficacy; (c) perform repeat thoracoscopic pleural inspection after talc insufflation to ensure even distribution of the powder over

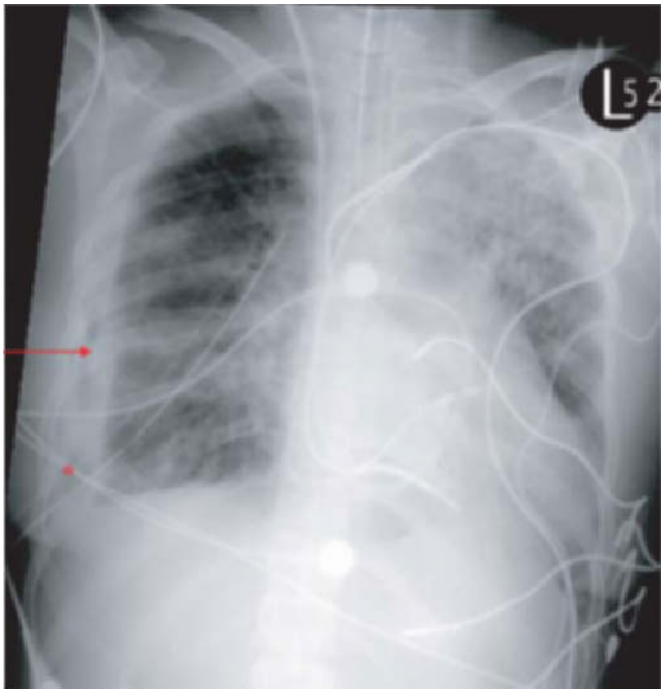

Figure 20.4 "Trapped" lung, complication of malignant pleural effusion. This figure shows a PA chest radiograph performed in an individual with diffuse right pleural malignancy and effusion status post insertion of a "standard" thoracostomy tube. Note the extensive visceral pleural thickening (arrow) and small, lateral pneumothorax *ex vacuo* (star). This patient is not a candidate for chemical pleurodesis, and can either be managed with surgical decortication, or with exchange for a tunneled pleural catheter to facilitate home drainage of the effusion. The choice of surgery versus Pleurx® is made on the basis of performance status and life expectancy.

the pleural surface; (d) insert the chest tube as low as possible in the thorax, directed posteriorly toward the costovertebral gutter and as close to the apex as possible for optimal drainage of residual fluid [18].

Therefore patients with MPE are good candidates for thoracoscopy talc pleurodesis if they meet the following criteria: (a) failure or unavailability of specific treatments; (b) dyspnea that improved after large-volume thoracentesis with subsequent and rapid recurrence of the pleural effusion; (c) absence of trapped lung as evidence by previous thoracenteses and control of intrapleural pressures. The pleural pH has some value in determining the candidacy of MPE patients for talc poudrage pleurodesis, as low pleural pH in MPE has been associated with advanced disease and trapped lung, which is a contraindication to pleural symphysis [48,49].

Management of MPE with "trapped lung"

The patients with MPE who are least likely to benefit from pleural drainage and chemical sclerosis are those with so-called trapped lung. These patients often have a dense peel of malignant tissue encasing the visceral pleura, and fail to exhibit complete lung reexpansion after drainage of the effusion [50] (Figure 20.4). Because apposition of the pleural surfaces cannot be achieved, sclerosis attempts are rarely successful and management for these patients has proved challenging. Therapeutic options include repeated thoracenteses, long-term thoracostomy drainage, pleurectomy/decortication, and pleuroperitoneal shunting [51]. Each of these techniques, however, carries with it specific risks and liabilities, and some may not be feasible for all patients.

Serial thoracenteses can provide immediate relief for symptoms resulting from chronic MPE and trapped lung, and has traditionally remained an option for patients felt to be unsuitable candidates for other therapies, especially those with limited life expectancy. However, as MPE usually recurs quickly, these patients may require frequent intervention. With repeated procedures, they are at increased risk for complications including pneumothorax, empyema, loculation of pleural fluid and hypoproteinemia. Long-term tube thoracostomy drainage offers some of the advantages

that are conferred by the Pleurx® catheter, namely the capacity for use in the home setting. However, semi-rigid chest tubes, sutured to the chest wall at the point of entry into the pleural space, cause discomfort and increase the risk of local infection. Additionally, patients may not have significant control over the timing or duration of drainage, requiring constant connection to a relatively bulky portable water seal drainage system. Accidental disconnection from the system may lead to a tension pneumothorax. Because of these considerations, extended-term tube thoracostomy drainage is infrequently utilized in the management of patients with MPE [51].

Pleuroperitoneal shunting may also allow some patients who are not candidates for definitive therapy with pleurectomy and decortication to achieve palliation of symptoms arising from recalcitrant MPE [52]. These shunts may be placed under general or local anesthesia and are tunneled subcutaneously, decreasing the risk of infection. Patients are required to perform manual compression of the pump chamber multiple times during the day for effective evacuation of the pleural space and to keep the shunt patent, requiring a time commitment of at least 20–40 min daily [53]. Potential complications include infection, malignant peritoneal seeding and small bowel obstruction. Shunt occlusion due to tumor ingrowth or fibrin debris has also been reported. Contraindications to pleuroperitoneal shunt placement include inability to operate the pump, multiple loculations or an obliterated peritoneal space [54–57].

Pleurectomy and decortication are generally considered to be definitive palliative therapy in the management of recurrent MPE with trapped lung. The high perioperative morbidity and mortality of pleurectomy and decortication preclude consideration of these procedures for most patients. Those who do undergo the procedure tend to have excellent preoperative functional status and significant life expectancy, having nevertheless failed other attempts at palliation [58].

In our experience, placement of a permanent PC for repeated drainage of symptomatic pleural fluid accumulations provides a convenient, effective alternative to the procedures currently in use for patients with refractory MPE and trapped lung. Most patients experienced relatively minor, if any, problems with chronic catheter use. Skin breakdown and insertion site infection typically respond promptly to wound care and oral antibiotics. Catheter infection and occlusion are potentially serious complications for which patients should be vigilantly monitored. As a relatively noninvasive procedure, PC placement may be reasonably performed in patients in whom other invasive procedures are contraindicated due, e.g. to somewhat limited life expectancy or metastatic abdominal disease. The PC is usually placed in the outpatient setting and may be largely maintained at home, minimizing time spent at office visits and in the hospital [56].

Conclusion

The development of MPEs in advanced malignancies can cause significant morbidity and can lead to progressive respiratory failure and death. Adequate drainage of MPEs with subsequent pleural symphysis can provide significant palliation for these patients. Several approaches are available to provide palliation, including repeated thoracentesis, chest tube drainage with chemical pleurodesis, VATS with chemical or mechanical pleurodesis and surgical pleurectomy/decortication (Figure 20.5). It is our opinion that tunneled, indwelling PCs are a cost-effective and desirable approach to the management of MPEs. They can be inserted on an outpatient basis without the subsequent pain, constitutional symptoms and hospitalization required for chest tube mediated chemical pleurodesis. Medical thoracoscopy offers the possibility to carefully explore the pleural cavity for the evaluation of pleural layers and perform biopsies for diagnosis and management of severe pleural adhesions to facilitate pleural symphysis by talc and proper placement of the chest tube for optimal drainage. Immediate talc poudrage can be done in case of macroscopic or extemporaneous histologic evidence of malignancy and ineligibility of the patient for trials on intrapleural treatment. As mentioned previously, each of these modalities has its limitations, and a more effective and less invasive approach for treating MPEs would be desirable. Crucial information regarding the relative benefits of varying approaches to MPE treatment may be forthcoming from the National Cancer Institute

Figure 20.5 Algorithm for MPE Management.

(NCI) sponsored multicenter, prospective clinical trial, CLB-30102, a Phase III randomized study of pleurodesis using a standard chest tube with talc slurry versus a small catheter for the treatment of symptomatic unilateral MPEs.

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21 CHAPTER 21

Management of spontaneous pneumothorax

Michael H. Baumann, MD

Pneumothorax classification and epidemiology

A pneumothorax is air within the pleural space. A textbook [1] and several journal reviews [2–4] classify pneumothoraces as traumatic or spontaneous in origin. Traumatic pneumothoraces result from direct or indirect trauma to the chest. A traumatic pneumothorax arising intentionally or unintentionally during a diagnostic or therapeutic medical intervention is termed an iatrogenic pneumothorax. Spontaneous pneumothoraces (SP), the focus of this chapter, occur without preceding trauma or other obvious precipitating cause.

Spontaneous pneumothoraces are sub-classified, somewhat arbitrarily, as either primary or secondary [1,3,4]. Primary spontaneous pneumothoraces (PSP) develop in patients without immediately apparent underlying lung disease. Secondary spontaneous pneumothoraces (SSP) occur in patients with underlying lung disease, e.g. chronic obstructive lung disease (COPD).

The study by Melton and colleagues [5] Olmsted County, Minnesota, of the incidence of pneumothorax provides information indicating that there are more than 20 000 new cases of SP in the United States each year. These events cost the health care system nearly $130 000 000 each year [3]. Cases of SP are roughly equally divided between PSP and SSP [5].

Etiology, recurrence rates and timing of recurrence prevention

There are a myriad of etiologies of SSP. Arguably, the majority of SSP are due to underlying COPD [3,4]. However, AIDS-related pneumothoraces, particularly those associated with *Pneumocystis carinii* pneumonia (PCP), have been suggested to be the leading cause of SSP in the urban setting [6]. Many other underlying lung diseases contribute to the develop of a SSP including, but not exclusively, cystic fibrosis, asthma, necrotizing pneumonias, various interstitial lung diseases (sarcoidosis, idiopathic fibrosis, Langerhans-cell granulomatosis), rheumatoid arthritis, malignancy and thoracic endometriosis [4].

The etiology of PSP is more controversial. A recent debate outlines the issues [7,8]. Although PSP arise in patients without immediately obvious underlying lung disease, closer inspection yields a likely etiology for pneumothoraces in many of these patients. Studies show more than 80% of computed tomography scanned patients [9] and up to 79% of patients undergoing surgical evaluation have emphysema like changes (ELC) (also called bullae or blebs) in the subpleural area that are potentially etiologic for PSP [10]. However, all evidence supporting ELC as the key etiologic cause of PSP is indirect and some argue that other etiologies need to be considered including a general "porosity" of the visceral pleural surfaces in PSP patients [7,11]. Regardless, a recent text [1] and

journal review [4] continue to support rupture of ELC as the etiology of PSP. Given that blebs and bullae (ELC) are the most immediately obvious cause of a PSP, they cannot and should not be easily dismissed [8].

The goals of treatment of SP are drainage of pleural air (when appropriate) and the prevention of future recurrences [3,12]. Recurrence prevention addresses purported underlying etiologic issues. As opposed to traumatic pneumothoraces [13], possible future recurrences of an SP are of considerable concern [1,2,4,14]. Reported recurrence rates following an SP vary considerably due to differences in duration of follow-up and treatment approaches [3,15]. A 1997 compilation of data in PSP patients without definitive recurrence prevention notes a mean recurrence of 30% with rates ranging from 16 to 52% [10]. Light and colleagues' controlled trial of SP patients randomized to either recurrence prevention by chest tube directed tetracycline sclerosis versus no prevention, reported a recurrence rate of 43% in SSP patients not undergoing recurrence prevention [16]. This largest SP controlled trial, to date, found that most recurrences occurred within the first 6 months of the initial event [16].

That the underlying etiology is a key SP management consideration is reflected in the recurrence prevention recommendations of an American College of Chest Physicians (ACCP) SP management guideline [12]. Integral to these guidelines is addressing underlying ELC noting that bleb/bullous resection in a patient with a PSP is the most appropriate approach. Specific recurrence prevention approaches, including the role of surgery, will be addressed in greater detail later in the chapter.

Timing of the recurrence preventative intervention is debated. Mortality with an initial or recurrent PSP is rare in patients with relatively normal lung function and accompanying good pulmonary reserve [14,17]. In contrast, an initial SSP or recurrence is more life threatening due to the underlying precipitating lung disease limiting the patient's pulmonary reserve. Age-matched COPD patients have a 3.5-fold increase in relative mortality with an SSP event [15], with reported mortality in COPD patients suffering an SSP ranging from 1 to 17% [16,18–20]. Light and colleagues' large randomized trial reports the lowest mortality of 1% [16]. Given this variance in recurrence associated mortality risk, the timing for prevention differs for PSP and SSP. Of the ACCP management guideline panel members 85% recommend that recurrence prevention for PSP be reserved for the second PSP occurrence. However, a patient's desire to continue in potentially high pneumothorax risk activities such as scuba diving or flying may warrant earlier PSP recurrence prevention. Alternately, 81% of panel members recommend a recurrence intervention after the first occurrence of an SSP. Notably, the ACCP guidelines, specifically focused only upon COPD-related SSP [12].

Diagnosis and treatment: general considerations and guideline options

The choice of a treatment for PSP or SSP must take into account the differing mortality and morbidity risks with both an initial and recurrent pneumothorax event and whether the treatment option affords any recurrence prevention. Management options not providing recurrence prevention include oxygen therapy, observation aspiration and chest tube placement (without introduction of a pleurodesis agent). Chest tube placement with introduction of a pleurodesis agent and various surgical approaches including thoracoscopy and thoracotomy provide varying degrees of recurrence prevention success. The myriad of management options has contributed to a heterogeneous approach to care by clinicians surveyed in the United States [14]. This heterogeneity prompted the ACCP to commission the development of the management guideline. Given the limited publication of high quality data, a Delphi survey approach limiting the bias of the participating expert panel was used to develop the ACCP guideline [12]. Although these guidelines provide direction to management and will be incorporated in the following management suggestions, treatment choices must still be tailored to individual patient requirements. The ACCP guidelines provide direction to the management of PSP patients and only SSP due to COPD. However, many of the suggestions for SSP management due to COPD could likely be extended to other etiologies of an SSP [12]. The British Thoracic Society has guidelines in

preparation to update their earlier publication in 1993 [21].

Given the nonspecific signs and symptoms associated with an SP, a high level of suspicion and a confirmatory chest radiograph are required to make the diagnosis. Identification of the visceral pleural line displaced from the chest wall on an upright chest radiograph is the key to diagnosis [4]. Expiratory chest radiographs add little additional information over a routine inspiratory chest film [22,23]. Some continue to utilize the diagnostic chest radiograph to calculate the percentage size of pneumothorax (percentage of hemithorax involved) to choose a treatment strategy [1]. However, the chest radiograph (and accompanying calculations based on various chest and pneumothorax dimensions) when compared with computed tomography is a poor tool to determine size [24]. Alternately, a recent analysis of PSP patients notes that calculations based on the chest radiograph are a good estimate of size [25]. This success may have been due to the fact that only first time PSP patients were included who may not be prone to asymmetric collapse of the lung. Recurrent PSP or SSP may collapse asymmetrically due to underlying pleural adhesions that developed during earlier occurrences and SSP patients may have asymmetric lung collapse due to their underlying lung pathology. The ACCP guidelines emphasize the combination of the degree of lung collapse determined by the distance of the visceral pleural surface from the chest wall in combination with patient symptoms to select an appropriate treatment option. The distance used to define a large ($\geq$3 cm lung collapse) or small ($<$3 cm) pneumothorax was defined by the ACCP Delphi expert panel [12] and is arbitrary, emphasizing the need to assess the level of patient stability in management choices.

Specific management options and considerations

Oxygen

Oxygen supplementation is a valuable and potentially overlooked therapeutic option in SP management. The role of oxygen therapy in SP management is, in fact, not addressed in the ACCP guidelines. Supplemental oxygen should be incorporated with most pneumothorax patients, regardless of etiology, as it will increase the pleural air reabsorption rate and help treat any accompanying hypoxemia. The baseline rate of pleural air absorption without supplemental oxygen is about 1.25% of the involved hemithorax per day [26]. Hence, if a patient suffers a 20% pneumothorax, approximately 16 days will be required for reabsorption of the pleural air if no additional air leaks into the pleural space. Supplemental oxygen increases this reaborption rate by three- to four-fold. The greatest increases are noted in patients with larger pneumothoraces [27,28]. Supplemental oxygen creates a gas pressure gradient between the tissue capillaries surrounding the pleural space and the pleural space enhancing pleural nitrogen reabsorbtion first and over time any other intrapleural gases [27,28]. Additionally, oxygen supplementation will treat the hypoxemia that can occur from a pneumothorax. Pneumothoraces induce changes in ventilation–perfusion relationships, anatomic shunt and dead space [29,30]. Improvement in these pneumothorax-induced changes may be delayed by 30–90 min after pleural air evacuation, with ventilation–perfusion relationships potentially worsening [30], further emphasizing the utility of oxygen supplementation.

Observation

Simple observation has been recommended by a current text as a treatment option for PSP patients occupying less than 15% of the hemithorax but is not suggested as a first line management choice for SSP [1]. Similarly, observation is the preferred ACCP guideline management option for stable PSP patients with a small pneumothorax ($<$3 cm collapse). Pleural drainage of some type is recommended for larger PSP ($\geq$3 cm lung collapse). PSP patients managed by observation should be monitored in the emergency department for 3–6 h and then discharged home if a repeat chest radiograph excludes pneumothorax progression. Within 12–48 h of discharge a follow-up chest radiograph should be obtained to document pneumothorax stability or improvement. Clinically stable SSP patients with a small pneumothorax may be managed by inpatient observation [12]. Rare

reports of death with observational management [31] emphasize the need for careful monitoring if observational management of any SP is chosen.

Simple aspiration

The technique of simple aspiration is variable. Light in his recent text suggests the insertion of a 16-gauge guide needle with a catheter inserted and the guide needle extracted leaving the catheter. A three-way stopcock and a 60-mL syringe are attached to the catheter and air is manually aspirated until no more can be aspirated or a total of 4 l is removed. Subsequently the catheter is secured to the chest wall and a chest radiograph obtained [1]. Technological refinements include all-encompassing kits and incorporation of a one-way valve (such as a Heimlich) attached to the catheter have simplified the procedure but clouded the concept of simple aspiration. These refinements to simple aspiration in effect transform it to placement of a small chest tube [3]. Despite the vagueness of definition, overall success (defined by lung reexpansion) of simple aspiration in SP studies, without clear separation of PSP and SSP patients, ranges between 53 and 58% [32,33]. Success in studies separating PSP and SSP appears to be about 75 and 37%, respectively [34–36]. Patients older than 50 years or in whom more than 2.5 l of air is aspirated are most likely to fail aspiration [37].

Simple aspiration is central to the management of spontaneous pneumothorax as described by the nearly ten-year-old British Thoracic Society guidelines [21]. Aspiration management is one of the few areas of SP management wherein randomized controlled trials exist; unfortunately these trials all have major flaws. Harvey and Prescott's study, as concluded by the authors, supports the use of aspiration [38]. However, this study did not define important design elements including the definition of outcomes, randomization methods and techniques of chest tube insertion. This is compounded by the fact that more patients with complete pneumothoraces were assigned to chest tube management as compared to simple aspiration. Lastly, the success of chest tube placement is not defined in the article although personal communication indicates that the percentage success was higher with chest tube placement than with simple aspiration. Andrivet and colleagues report a higher success rate with chest tube placement compared with simple aspiration (93 versus 67%; $p = 0.01$). The authors conclude that thoracic drainage "via a chest tube was significantly more effective in the treatment of pneumothorax" than simple aspiration [39]. This article is flawed by a convoluted two-arm aspiration enrollment, with one arm not incorporating randomization, making interpretation difficult.

The most recent randomized trial provides the most promising support for simple aspiration versus chest tube placement in first time PSP [40]. Noppen and colleagues studied 60 PSP patients and concluded equivalency of success (lung reexpansion) for aspiration versus chest tube placement. The accompanying editorial highlights another key finding noted by the authors [40]. If manual aspiration fails, a second aspiration is not likely to succeed and likely represents a persistent air leak. The study however has major flaws not highlighted in the editorial. Success in the aspiration and chest tube groups was not similarly defined. Partial or complete lung reexpansion was "success" for the aspiration group while complete reexpansion was required to be defined as a "success" in the chest tube group. Also, the aspiration catheter was not managed the same throughout the aspiration group. There were fewer current smokers in the aspiration group (10 of 27, 37%) than in the chest tube group (25 of 33, 76%). Next, the power analysis noted that there was up to an approximate 75% probability that a meaningful difference in endpoints was overlooked, indicating that equivalency of the two arms is doubtful. Intention to treat kept all aspiration patients in the aspiration arm. This negated the success created by placing a chest tube in patients failing aspiration from being ascribed to the chest tube arm but instead to aspiration. Lastly, the chest tube group was not offered the option of home care with placement of a one-way valve (Heimlich valve), requiring all chest tube patients to undergo admission [40,41].

The limited quality of the published information supporting aspiration explains the minimal role for aspiration in the ACCP guidelines [12]. This minimal role for aspiration is unlikely to change following the recent publication of Noppen and colleagues [40]. The ACCP guidelines

strictly defined simple aspiration as the insertion of a needle or cannula with the removal of pleural air followed by the immediate removal of the needle or cannula [12]. As defined, simple aspiration is not appropriate for most clinically stable PSP patients with a small pneumothorax unless the pneumothorax enlarges during observation. Modification of simple aspiration including placement of a catheter, subsequent aspirations, continued catheter residence and attachment to a Heimlich valve device may be acceptable in certain circumstances, however this equates to placement of a small bore chest tube. The certain circumstances include large pneumothoraces in a stable PSP or SSP patient. A clinically unstable patient with a large PSP may undergo aspiration with subsequent Heimlich valve attachment and overnight hospital monitoring. However, preferred management in this setting is chest tube placement and admission to the hospital [12].

Chest tube placement and removal

Chest tube placement assumes a pivotal role in initial SP management under the ACCP guidelines. Initial chest tube placement and admission to hospital is preferred management for unstable patients with a large PSP or for any SSP patient with a large pneumothorax or clinical instability [12]. Appropriate chest tube size selection is key, and consideration of the magnitude of a potentially coexisting persistent air leak integral to the correct size choice. The Fanning equation reflects the variables that determine the flow of moist gas with turbulent flow characteristics through a chest tube as is the case with any pneumothorax ($v = \pi^2 r^5 P/fl$; v = flow, r = radius, l = length, P = pressure, f = friction factor) [3,42–44]. Airflow through a chest tube is primarily determined by the radius of the tube and is directly proportional to the radius to the power of five. Flow is inversely proportional to the length of the tube to the power of one. Large airflow rates may be of particular concern in mechanically ventilated pneumothorax patients [45].

The ACCP statement takes these issues into consideration and makes chest tube (catheter) size recommendations [12]. A small-bore catheter ($\leq$14 F) or smaller bore chest tube (16–22 F) should be considered in PSP chest tube candidates (not often at risk for persistent large air leaks). Larger bore tubes (30–36 F) are inappropriate for PSP patients. Given their underlying lung disease, SSP patients may have a greater risk of a larger air leak and also may be more likely to require mechanical ventilation. Therefore, stable SSP patients without great risk of a large air leak (not mechanically ventilated) who are chest tube candidates, should have a 16–22 F chest tube placed. Smaller bore tubes ($\leq$14 F) may be acceptable in selected patients [12]. This may conceivably include those patients refusing a larger bore tube and those with greater bleeding risks that may be partially obviated with the Seldinger (over guide wire) placement of a smaller bore tube. Unstable SSP patients and patients on mechanical ventilation should have a 24–28 F chest tube placed.

Subsequent management of a chest tube once placed is quite variable in the literature and in practice [3,14]. Much debated is the value of suction immediately after chest tube placement for a pneumothorax. So and Yu found no advantage to suction in 53 episodes of SP [46]. Minami and colleagues' study incorporating a Heimlich valve in combination with a small bore catheter and no suction supported this finding [47]. More than 77% of SP patients in Minami and colleagues' study had full lung reexpansion and no air leak without suction. The ACCP guidelines recommend attaching the chest tube to a water seal device with or without suction in most SP patients. If the lung does not reexpand promptly, suction then should be applied. A Heimlich valve or similar one-way valve device may be used in selected stable SP patients instead of a water seal device. However, a water seal device is a better option in most SSP patients according to consensus [12].

Upon resolution of the pneumothorax and any associated air leak, and after recurrence prevention options are addressed, the technique of chest tube removal is the next consideration. This has been a particularly heterogeneous area of practice in the United States, with no clearly defined approach [14]. Most controversial seems to be the role of chest tube clamping prior to its removal as a tool to ensure the absence of small air leaks not readily detected by monitoring the water seal chamber of the pleural drainage device for evidence

of ongoing bubbling. U.S. thoracic surgeons [14] and British physicians [48] do not incorporate clamping while U.S. pulmonologists favor its use [14]. Those opposed to clamping raise concerns for the development of unnoticed lung collapse [48]. "Clamping" supporters note that air leaks may not be obvious in the air leak indicator chamber, and clamping with proper monitoring instructions may detect a small air leak and avoid chest tube replacement due to an overlooked air leak [49].

This debate was not definitively solved by the ACCP consensus guidelines. The consensus group was roughly divided regarding the advisability of clamping, with 47 and 59% incorporating clamping as part of the chest tube removal sequence in PSP and SSP, respectively. If clamping is utilized, the tube should be clamped for approximately 4 h in PSP and 5–12 h in SSP with a subsequent chest radiograph obtained to assess for air reaccumulation [12]. Given the continued clamping controversy, its associated potential patient safety issues, costs related to chest tube replacement and prolonged hospitalization, this area needs further study.

Chest tube and pleural drainage unit facts

The ACCP guidelines provide suggestions regarding the size of chest tubes to be placed and when and how to incorporate a pleural drainage unit (PDU). Unfortunately, this does not complete the necessary information the clinician needs to know in utilizing these devices. Not all small-bore catheters and PDU are of equal efficacy in their ability to handle various airflows [50]. Flow rates of commercially available catheters found in pneumothorax and thoracentesis catheter kits vary significantly. As expected from the Fanning equation (given earlier), smaller bore catheters accommodate lower flow rates, e.g. 8 F catheter flows range from 2.6 to 5.5 l/min at −20 cm of water suction. The 8 F thoracentesis catheters handle significantly lower flows than their 8 F pneumothorax counterparts manufactured by the same company even though they are shorter in length. This appears to be due to hardware found proximally on the thoracentesis catheters. Of greater consequence are the significantly lower flow rates delivered by the larger bore Cook® catheters (Bloomington, IN) (16 F, 14.8 l/min) and smaller bore Cook® catheters (14 F, 12.8 l/min) compared with the 14 F Arrow® catheters (Mississauga, Ontario) (16.8 l/min; $p < 0.05$). These flow rate differences in identical bore catheters may represent differences in catheter lengths (both Cook® catheter lengths are greater than their Arrow® counterparts), side hole variations and perhaps true bore differences. Appropriate size selection of a chest tube may also be thwarted by inappropriate PDU selection. Commercially available PDU flow rates range from 10.8 to 42.1 l/min at −20 cm of water pressure. Similarly, the accuracy of the measured level of negative pressure delivered (suction) varies significantly although the magnitude of these inaccuracies is likely of little clinical significance [50]. These flow rate differences of chest drains and PDU could be particularly important in SSP patients who are mechanically ventilated or unexpectedly require mechanical ventilation with its potential to create large air leaks.

Persistent air leak management

Once a chest tube is in place, the possibility of a continued air leak (bronchopleural fistula) arises. Such a leak may be found in up to 18% of PSP and 40% of SSP patients 48 h after chest tube placement [51]. Estimates as to how long to monitor an air leak (bronchopleural fistula) vary widely. Primary data focused on this question suggest monitoring from 2 to 14 days [51–54]. Light suggests placing a second chest tube in 48 h if the lung has not reexpanded in a PSP patient initially treated with a small bore catheter. Then, if the lung has not reexpanded or a bronchopleural fistula persists after 3 or 4 days consideration should be given to a more invasive procedure. This equates to monitoring a PSP for up to 7 days. If the lung does not reexpand in 3 days or if there is a persistent air leak for more than 3 days consideration should be given to a definitive intervention in an SSP patient [41]. Such variability explains the wide range of practice habits in the United States with more than 75% of physicians surveyed monitoring a persistent air leak for 5–10 days before pursing a definitive intervention in 1997 [14]. The ACCP guidelines suggest monitoring a PSP for up to 4 days and an SSP for 5 days before moving to a definitive intervention [12].

Whatever observation period is chosen, the patient should be assessed daily, mindful that timely definitive intervention may limit morbidity and costs from the underlying process and prolonged hospital stay. Waller and colleagues report a significantly decreased thoracoscopic operative success directly proportional to preoperative delay, often from initial extended chest tube management, compounded by a 4-day increase in the postoperative stay in SP patients [55]. A preoperative SP-associated air leak itself is a predictor of decreased thoracoscopy success in Matsuzoe and colleagues' study [56].

The ACCP consensus statement [12] and a recent text [1] recommend a surgical intervention for a persistent air leak in both PSP and SSP. A myriad of publications tout the apparent success and merits of a thoracoscopic approach, medical or surgical, but no randomized controlled comparative trial of thoracoscopy versus thoracotomy (any approach including limited axillary) has clearly established either procedure's superiority. However, the ACCP statement suggests thoracoscopy as the preferred approach for either PSP or SSP with a persistent air leak and for SP recurrence prevention (see following section for further details regarding recurrence prevention).

Surgical recurrence prevention and surgical issues

Overall, recurrence prevention success rates for a surgical approach ranges from 95 to 100% [3]. Surveyed physicians frequently chose a surgical approach for SP recurrence prevention and for a persistent air leak, with a thoracoscopic approach more frequently chosen than a thoracotomy approach [14]. Recurrence prevention success of a thoracoscopic approach is generally less than that provided by a thoracotomy. Recurrence rates after video-assisted thoracoscopic surgery are from 2 to 14% and from 0 to 7% after limited thoracotomy [4].

As noted, although no randomized comparisons clearly demonstrate superiority of thoracoscopy, the ACCP consensus group suggests thoracoscopy as the preferred approach for SP recurrence prevention [12]. A thoracoscopic approach to PSP or SSP should include intraoperative bullectomy performed by a staple device. Intraoperative pleurodesis should be performed with parietal pleural abrasion limited to the upper half of the hemithorax for both PSP and SSP recurrence prevention. Interestingly despite talc's apparent popularity among clinicians [14,57], no consensus was reached among the Delphi consensus group for the role of talc poudrage in PSP patients for recurrence prevention. However, parietal pleurectomy, with some consensus, is felt to be an acceptable alternative pleurodesis approach in PSP patients. For SSP patients, muscle-sparing (axillary) thoracotomy is an acceptable alternative to a thoracoscopic recurrence prevention and parietal pleurectomy limited to the upper half of the hemithorax being an additional preferred pleural symphysis technique. Talc poudrage, with some consensus, may be used in an SSP for pleural symphysis [12].

Multiple consecutive patient enrollment series' during the last 5–10 years incorporating thoracoscopy to manage patients with SP and other chest diseases have fueled thoracoscopy's popularity. However, randomized controlled trials comparing thoracotomy (limited or otherwise) to thoracoscopy management of SP patients are quite limited. Waller and colleagues provide the only randomized controlled trial (sixty patients) comprehensively comparing video-assisted thoracoscopic surgery to thoracotomy (posterolateral) approach to spontaneous pneumothorax patients [58]. Postoperative decline in pulmonary function, FEV_1 ($p < 0.05$) and FVC ($p < 0.01$), is significantly greater in the thoracotomy group. However, intraoperative time is significantly greater ($p < 0.05$) in the thoracoscopy group and no differences in analgesic use, chest tube drainage days, postoperative length of stay or death are noted. During a mean follow-up period of 15 months, no significant difference in pneumothorax recurrence for thoracoscopy (6.7%) and thoracotomy (3.3%) approaches was uncovered. One out of thirty patients (3.3%) undergoing thoracoscopy required conversion to thoracotomy [58]. (In comparison, a range of 2–10% of PSP and up to 29% of SSP patients undergoing thoracoscopy have been reported to require conversion to thoracotomy due to technical difficulties [4].) No significant difference in blood loss or in-hospital deaths was noted between thoracoscopy and thoracotomy

patients. Three deaths occurred and were in an elderly subgroup of SSP patients, one in the initial thoracoscopy group and two in the thoracotomy group [58].

Waller subsequently published a follow-up nonrandomized assessment wherein thoracoscopy is the treatment of choice for SP, with thoracotomy reserved for thoracoscopy technical failures that emphasize the significant learning curve for the thoracoscopic approach to SP patients [59]. There is no statistical comparison of PSP to SSP within the thoracoscopy group in the initial study but operating time and postoperative length of stay appeared longer in SSP patients by a mean of 12 min and 5 days, respectively [58]. Similarly, the follow-up study found that thoracoscopic operative times and postoperative length of stay are statistically significantly longer by a mean of 12 min ($p = 0.001$) and 5 days ($p < 0.001$), respectively, for SSP compared to PSP patients. There are no significant differences in the thoracoscopic treatment failure rate (<30 days) between PSP and SSP patients. Over time, thoracoscopic operating times ($p < 0.001$) and postoperative stay ($p = 0.01$) significantly decreased as experience increased with PSP patients but not with SSP patients. Thoracoscopic operative failure, in aggregate, fell significantly with increasing experience ($p = 0.03$). Notably, Waller highlights that more careful patient selection led to a fall in the proportion of SSP undergoing operations and an increase in alternatives including closed chemical pleurodesis [59].

Two other studies warrant brief mention. Kim and colleagues [60] performed a similar comparative study as Waller and colleagues [58], but without strict randomization, confirming a lack of superiority of video-assisted thoracoscopic surgery over thoracotomy. Sekine and colleagues' randomized comparison of video-assisted thoracoscopic surgery versus axillary thoracotomy in SP patients ($n = 38$) notes no difference in operative times or postoperative drainage days. Postoperative length of stay, pulmonary function and recurrence rates are not reported. Questionably clinically important differences in postoperative gas exchange are found in favor of thoracoscopy [61]. To date, no other prospective randomized comparisons of thoracoscopy and thoracotomy for SP appear to be available.

In total, these surgical studies indicate that thoracoscopic approaches to SP patients remain popular and are successful but not complication free. A prospective randomized comparison substantiating superiority of thoracoscopy over thoracotomy in operative times, postoperative pain control, postoperative length of stay, initial failure rates and late recurrences is wanting. Perhaps, a prospective randomized comparison of thoracoscopy versus thoracotomy today in SP patients in Waller's experienced hands would prove thoracoscopy superior, at least for PSP patients, in operative time, postoperative length of stay, economic parameters and conceivably in other key clinical parameters including complications.

Choice of a pleurodesis agent

Although according to the ACCP consensus a surgical approach is preferred for SP recurrence prevention [12], those patients initially receiving a chest tube have the opportunity to undergo pleurodesis induced recurrence prevention. Success rates with chemical pleurodesis are only 78–91% compared to the success rates of 95–100% with surgical interventions [3]. Chest tube directed pleurodesis is acceptable for PSP recurrence prevention in those patients wishing to avoid a surgical approach and those with increased surgical risk (e.g. bleeding diathesis). Similarly, chest tube directed pleurodesis for SSP patients may be warranted for certain circumstances based upon a patient's contraindications to surgery, management preferences and underlying disease related poor prognostic factors [12].

The choice of pleurodesis agent continues to be debated with the role of talc central to the debate [62,63]. Success appears highest with talc when compared to other available agents [3,62], but concerns over talc-associated respiratory failure and death remain [63]. The occurrence of talc-related respiratory failure is quite low, 0.71% in use for recurrent pleural effusions (talc slurry or poudrage) and 0.15% for pneumothorax (talc poudrage) [62], and may be overplayed in the literature. Predictors for talc-related problems may include small particle size [64,65], and, at least in the setting of malignant pleural effusions and talc poudrage, prior pleural biopsy [64]. Talc, despite these issues, remains a popular pleural sclerosant

internationally [57]. The ACCP statement notes that if chemical pleurodesis is performed for PSP or SSP, doxycycline or talc slurry is preferred [12]. Appropriate informed consent should be provided whatever the pleurodesis agent chosen.

Role of medical thoracoscopy and computed tomography in SP patients

Particularly germane to a text on interventional pulmonology is the role of medical thoracoscopy (pleuroscopy) in the management of SP patients. Prior discussions in this chapter have focused on the role of video-assisted thoracoscopic surgery. Compared to video-assisted thoracoscopic surgery, medical thoracoscopy uses fewer chest entry ports (often only one), and local anesthesia with conscious sedation as opposed to general anesthesia often incorporating a double lumen endotracheal tube. Medial thoracoscopy may be performed successfully in the bronchoscopy suite as opposed to the necessity of a formal operating room or surgical suite for video-assisted thoracoscopic surgery. In the mid-1990s approximately 5% of surveyed practicing pulmonologists performed medical thoracoscopy [66], although the popularity of thoracoscopy-related lectures at recent national meetings might indicate the percentage is rising. Controversy surrounds the role of the pulmonologist and other non-surgeons performing medical thoracoscopy although forthcoming guidelines from the ACCP outlining suggested minimal training requirements will hopefully quiet the controversy. Regardless, any non-surgeon performing thoracoscopy for any reason including SP should maintain a close working relationship with their thoracic surgeon colleagues [67,68].

The role of medical thoracoscopist may be limited by the comfort level the thoracoscopist has manipulating the lung itself. As outlined earlier, the ACCP statement recommends elimination of underlying ELC (also called bullae or blebs) by staple bullectomy for adequate recurrence prevention [12], although (earlier) some argue such lung changes, especially in PSP, are without etiologic significance [7,11]. However, evaluation of the available literature may discern a potential role for the medical thoracoscopist not comfortable with manipulating the underlying lung.

Staging of ELC is often performed during thoracoscopic management of SP patients. Macroscopic stages seen during thoracoscopy of underlying ELC in SP patients often used are: Stage I, normal visceral pleura; Stage II, some pleural adhesions; Stage III, blebs or bullae (ELC) less than 2 cm in size; and Stage IV, bullae more than 2 cm in diameter [69–71]. SP patients are roughly divided between those that will be either Stage I or II and those that are either Stage III or IV [71]. Combining this information with recent publications of those touting the success of talc poudrage alone for the management of SP recurrences [69,70], a plan for the interventional pulmonologists not wishing to perform bullectomy may be possible.

Medical thoracoscopy in the hands of Tschopp and colleagues utilizing talc poudrage alone without any surgical intervention for ELC provides 95% recurrence prevention during a mean follow-up of 5 years in a mixed population of PSP and SSP patients. However, ELC likely play a role in recurrence given a higher pneumothorax recurrence risk in patients with bullae bigger than 2 cm (17% of patients, stage IV) compared to those without such bullae ($p = 0.03$, odds ratio of 7, confidence interval of 3.7–13.3) [69]. Similarly, Noppen and colleagues find a 6.5 and 8.7% recurrence rates in PSP and SSP patients, respectively, undergoing thoracoscopic talc poudrage alone. However, all ELC greater than 2 cm (stage IV) were treated with thermocoagulation [70].

In the aggregate, these two studies provide guidance to the medical thoracoscopist wishing to provide thoracoscopic directed recurrence prevention to SP patients but uncomfortable with ELC elimination options. Talc poudrage alone in SP patients with smaller ELC (<2 cm, stage III), no ELC or no adhesions (stage I–II, respectively) provides good recurrence prevention. Such an approach obviates surgical lung manipulation to eliminate ELC. Alternately, thermocoagulation (electrocautery), as incorporated by Noppen and colleagues [70], is far less invasive and technically challenging than staple bullectomy and provides a more accessible addition to talc poudrage for the medical thoracoscopists managing SP patients with blebs greater than 2 cm (Stage IV).

For the thoracoscopist not comfortable with either staple or electrocautery ELC removal

(bullectomy) knowledge of the underlying lung anatomy prior to chest entry is requisite. The ACCP guidelines do not recommend the routine use of computed tomography of the chest in patients with a first time PSP. The panel did not achieve consensus regarding the utility of computed tomography of the chest in PSP patients with recurrence, persistent air leaks or planned surgical interventions. Alternately, computed tomography of the chest is acceptable in SSP patients with recurrence, during air leak management, and for planning a surgical intervention. However, no consensus regarding computed tomography's role in SSP patients with a first occurrence was reached [12]. Regardless of these ACCP suggestions, the computed tomography may be too insensitive to find ELC of interest to the medical thoracoscopist wishing to avoid bullous removal procedures. In Horio and colleagues' PSP patient study 28 and 23% of the bullectomy alone and bullectomy with electrocautery groups, respectively, had no identifiable bullous changes by chest-computed tomography preoperatively. However, bullous changes were found intraoperatively in all patients [72]. The computed tomography protocol utilized is not indicated and may have been inadequate. Such information should temper the enthusiasm of a medical thoracoscopist not possessing ELC removal skills and who relies upon the computed tomogram of the chest to uncover Stage IV changes, wishing to manage SP patients thoracoscopically.

AIDS-related pneumothorax

The increasing likelihood of an AIDS-related pneumothorax occurring in the urban setting [6] warrants a brief review regarding their management. Thirty-six percent of SSP in patients admitted to Parkland Memorial Hospital (Dallas, TX) were due to AIDS, with the majority due to PCP. Up to 2.0% of AIDS patients, unrelated to procedures or mechanical ventilation, may suffer an SSP. Mortality from an AIDS-related pneumothorax unrelated to volutrauma varies widely, 10–50% [73–75]. Mortality may be particularly high in those patients with AIDS related pneumothoraces due to volutrauma (up to 100%) [75].

The limited survival prospect of this pneumothorax patient group compounds their frequent severe immunosuppression. Therefore the least invasive, safest, therapeutic option with the greatest success and the shortest length of stay is advised [76]. Supporting this approach are several publications incorporating a Heimlich valve to facilitate outpatient management [77–79]. The most recent of these notes that patients managed by conversion to Heimlich valve have a shorter mean length of stay after conversion compared to those patients managed conventionally by chest tube placement and thoracotomy. Mortality appeared higher in those patients managed conventionally than in the Heimlich valve conversion group (29.7 versus 20%, respectively) and there appeared to be greater pneumothorax resolution in patients managed by Heimlich valve than conventionally (100 versus 55%, respectively) [77]. Not answered by this publication or any others is the success and safety of using a drainage catheter and Heimlich valve as initial therapy in AIDS-related SP [76]. However, the Heimlich valve option is intriguing given it would offer a relatively noninvasive approach allowing the opportunity of early outpatient management.

The role of surgery in AIDS-related pneumothorax is clouded by an apparent reluctance to offer surgical options in these patients perhaps related to the potential risk to the operative team [76]. Additionally, nearly 40% of AIDS-related pneumothoraces with a persistent air leak may resolve when treated with chemical pleurodesis [80]. Regardless, considerable success may be achieved surgically in AIDS-related pneumothorax patients. Wait reports a 94% success for video-assisted thoracoscopy and talc poudrage in AIDS-related pneumothorax [81]. Some surgical studies that include advanced AIDS patients with pneumothoraces emphasize early surgical intervention noting limited operative mortality and morbidity [82–84].

Timely therapeutic decisions are crucial in the setting of a persistent air leak. The physician should daily consider making definitive intervention based upon the patient's risks and after discussion of the options with the patient. Based on Schoenenberger and colleagues' study of COPD-related pneumothoraces demonstrating a peak resolution at 48 h [51], I opt for early intervention [76]. The intervention may entail a surgical approach, discharge with a Heimlich valve in place, or continued in-hospital care with a chest tube depending upon the patient's circumstances.

Summary treatment approach

Based upon the ACCP guidelines [12], management of individuals with PSP is focused on selection of patients who may be treated with supplemental oxygen and simply observed. These patients include those with a small pneumothorax (<3 cm lung collapse) who are clinically stable. PSP patients with a large pneumothorax (≥3 cm lung collapse) whether stable or unstable should be considered for chest tube placement. Small (≤14 F) or moderate size chest tubes (16–22 F) are appropriate in this setting. A persistent air leak should be watched for no more than 4 days and recurrence prevention considered during the second pneumothorax event. A thoracoscopic approach is the preferred method of intervention for a persistent air leak and for recurrence prevention.

Arguably, COPD is the most common cause of SSP. As opposed to PSP patients, observation is not the focal point and inpatient management with chest tube placement pivotal for initial care [12]. Observation should only be used in SSP patients with small pneumothoraces (<3 cm lung collapse) and only as inpatients; chest tube placement is an alternative in these inpatients. Chest tube placement is preferred for SSP patients with large pneumothoraces regardless of stability. Stable SSP patients with a large SSP should be managed with tubes less than or equal to 14 F or 16–22 F. Unstable SSP patients and those mechanically ventilated (or likely to be ventilated) should be managed with 24–28 F tubes. A persistent air leak should be watched for no more than 5 days and recurrence prevention considered with the first pneumothorax event. As with PSP patients, a thoracoscopic approach is the preferred method of intervention both for a persistent air leak and for recurrence prevention.

AIDS-related SSP may be a common cause of SSP in urban areas [6]. Key to management of these patients with limited life expectancy and a persistent air leak is consideration of outpatient care utilizing a Heimlich valve attached to a drainage catheter or prompt surgical intervention.

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22 CHAPTER 22

Obstruction of the central airways: evaluation and management

William Lunn, MD

Introduction

Patients with central airway obstruction present the treating physician with a significant diagnostic and therapeutic challenge. Many patients experience an insidious onset of symptoms and a proper diagnosis is often delayed. It is common for patients to be treated for asthma or chronic obstructive pulmonary disease (COPD) for months or even years before a diagnosis of obstruction of the central airways is discovered. Moreover, once the diagnosis is established, the physician must choose among a wide array of management options.

The purpose of this discussion is to provide the reader with an understanding of the presentations of central airway obstruction and an appreciation of the various management options that are currently available.

Anatomical considerations

Physicians dealing with obstruction of the central airways must have a thorough understanding of the anatomy and physiology of the respiratory tract. Experts often employ the term "upper airway" to designate the hypopharynx, the pyriform sinuses and the larynx. The larynx is a complex organ with a three-fold function: to allow for ventilation, to protect the respiratory tract from aspiration and to allow for communication through phonation. The larynx is made up of nine cartilages that include the epiglottis, the thyroid, the cricoid, the arytenoids, the corniculates and the cuneiforms. These cartilages are joined by a series of muscles and ligaments and receive structural support from the hyoid bone, which is located anterior to the epiglottis and the base of the tongue [1]. The arytenoids are paired structures attached to the vocal ligaments and are responsible for movement of the vocal folds. The arytenoids are joined to the cricoid cartilage by a pair of synovial joints, the cricoarytenoid joints. The vocal folds measure approximately 15 mm in the adult male and 10 mm in the adult female [2]. The ventricular bands, or false vocal cords, span the arytenoids and the petiole of the epiglottis and are critical in protecting the larynx and trachea from aspiration. The introitus of the larynx is triangular in shape with the apex of the triangle formed by the joining of the vocal folds at the anterior commissure. The vocal folds form the sides of the triangle and the base of the triangle, known as the posterior commissure, is made up of the cuneiform and arytenoid cartilages. The subglottic space begins at the inferior margin of the vocal folds and ends at the distal end of the cricoid cartilage. The height of the larynx from the vocal folds to the proximal trachea measures approximately 25 mm in the average adult. The major nerve supply of the larynx includes the superior laryngeal nerve and the recurrent laryngeal nerves. The superior laryngeal nerve supplies sensory fibers to the pyriform sinuses, the vallecula, the epiglottis, the aryepiglottic folds and the dorsum of the vocal folds. This nerve also supplies a motor branch to the cricothyroideus muscles, which are involved in swallowing and tensing of the vocal ligaments. The

recurrent laryngeal nerves supply sensory branches to the ventral portion of the vocal folds and the entire subglottic larynx. The recurrent laryngeal nerve innervates all the intrinsic muscles of the larynx. It is important to note that these nerves enter the larynx at the cricothyroid joint, and in most cases, the nerve passes behind the joint. However, in 10–15% of cases, the nerve passes anterior to the joint and may be more vulnerable to pressure induced injury from within the laryngotracheal lumen [1,2].

The term "lower airway" is usually reserved for the trachea and main-stem bronchi. The trachea is made up of incomplete cartilage rings joined by fibrous tissue and smooth muscle. The cartilages are "U shaped" and measure approximately 4–5 mm in height. The posterior tracheal membrane is made up of two layers of smooth muscle: an inner transverse layer and an outer longitudinal layer. The posterior tracheal membrane lies adjacent to the anterior membrane of the esophagus. This combination of cartilage, muscle and connective tissue gives the trachea a firm, yet flexible quality that allows it to remain patent during periods of increased pleural pressure. The length of the adult trachea measures slightly longer than 11 cm and the diameter ranges from 16 mm in the female to 19 mm in the male. The right main-stem bronchus measures 12 mm in diameter and 25 mm in length on average. The left main-stem bronchus measures 10–12 mm in diameter and approximately 50 mm in length [3]. There are many vital structures that lie in close proximity to the trachea and main-stem bronchi of which the endoscopist must be aware. Anterior to the right main-stem bronchus lie the pulmonary arteries and veins, the azygous vein and the right bronchial artery, while the superior vena cava and the esophagus are located posteriorly. Anterior to the left main-stem bronchus lie the pulmonary arteries and veins, the arch of the aorta, the left recurrent laryngeal nerve and the left bronchial artery while the descending aorta and the vagus nerve occupy a posterior position.

Diagnosis

Central airway obstruction may be acute (foreign body aspiration) or chronic (endobronchial carcinoma). The physician must focus on the history in order to successfully diagnose and manage patients with these disorders. It is our practice to take a detailed history that includes ascertaining the symptoms the patient describes, the severity of the symptoms, their duration, palliative or exacerbating maneuvers, the exercise tolerance, the presence of arthritic conditions, previous surgeries including surgeries involving the head and neck, history of respiratory tract infection, previous experiences with critical illness and previous attempts to evaluate or treat central airway obstruction. The importance of obtaining and reviewing old medical records cannot be emphasized enough.

Signs and symptoms

Patients with central airway obstruction often present with dyspnea both at rest and with exertion. Patients with coexisting lung disease, such as COPD, may be more symptomatic from lesser degrees of airway obstruction than an otherwise healthy patient. Indeed, it is interesting to note that most patients without chronic lung disease do not complain of dyspnea until the lumen of the central airway is obstructed by approximately 50%. Patients with chronic lung disease may escape early diagnosis of central airway obstruction because their symptoms are ascribed to their preexisting lung disease.

Wheezing is a common symptom of central airway obstruction and may sound polyphonic if located in the main-stem bronchi. Monophonic wheezing should alert the physician to the possibility of tracheal or main-stem obstruction. Lesions of the larynx may cause stridor, dysphonia or dysphagia while lesions of the trachea and main-stem bronchi may cause dysphagia, chest discomfort, orthopnea or hemoptysis.

The patient with obstruction of the central airways often appears anxious with labored breathing. The astute physician will note the presence of accessory muscle use, sternal retraction, extension of the neck, digital clubbing and peripheral cyanosis.

Radiographic studies

A standard two-view chest radiograph should be obtained in all patients with suspected central airway obstruction. Berkmen [4] and

Dennie *et al.* [5] have reported that the central airways are often overlooked on a standard posteroanterior chest radiograph. Patients with suspected laryngeal pathology may benefit from a lateral soft tissue plain film of the neck. This provides a sagittal view of the airway from the nasopharynx to the cervical trachea. Tomography is also very useful in visualizing obstructions in the larynx and trachea [6].

Computed tomography (CT), both conventional and high-resolution technique, provides detailed morphology of the larynx and trachea and has enhanced the ability to diagnose and treat patients. Many investigators now consider CT to be the imaging modality of choice for patients being evaluated for airway obstruction [6]. New software has allowed for the development of virtual bronchoscopy in which CT generated images display the trachea and bronchi from the perspective of an endoscopist [7]. Though the role of virtual bronchoscopy in routine medical practice remains uncertain, it may prove to be a useful technology for assisting the endoscopist in thoroughly planning an intervention prior to bringing the patient to the endoscopy suite.

Magnetic resonance imaging (MRI) has particular utility in evaluating the larynx and proximal trachea [8]. The soft tissues of the larynx are well visualized with this technique. MRI is also useful in evaluating the mediastinum, especially when there is a hilar mass, as this technology readily differentiates vascular structures and soft tissue masses [9].

Flow volume loops

The flow volume loop (FVL) is essential in the evaluation of central airway obstruction and may provide the physician with the only objective estimate of the severity of airway obstruction before endoscopy is performed [10]. A FVL plots flow rate (l/s) against volume (l). The patient is asked to inhale to total lung capacity (TLC), forcibly exhale to residual volume (RV), and then rapidly inhale back to TLC. Many variables are derived from the FVL including the forced expiratory volume in 1 s (FEV_1), the forced vital capacity (FVC), and the flow at 50% of exhaled volume (V_{max50}). It is the shape of the FVL that is important in central airway obstruction rather than the absolute value of any of the variables.

In their seminal article, Miller and Hyatt demonstrated that airway obstruction could be simulated in normal volunteers by having them breathe through orifices of decreasing diameter [11]. A series of FVLS were generated by these subjects demonstrating an association between decreased airway diameter and diminished flow rates, as well as a corresponding "plateauing" of the expiratory and inspiratory limbs of the loop. Notably, the orifice diameter had to be decreased to 6 mm before the FEV_1 declined significantly. Patients with preexisting lung disease may not be able to generate a "classic" FVL when they are suffering from obstruction of the central airways because of an inability to generate high flow rates [12].

Endoscopy

The gold standard for the evaluation of central airway obstruction remains diagnostic bronchoscopy [13]. Endoscopy allows the physician to locate the lesion, obtain measurements of the diameter and length of the lesion, assess the impact of spontaneous respiration on the lesion and evaluate surrounding tissues. An assessment of vocal fold mobility is critical in dealing with patients with central airway obstruction. Especially with laryngeal and proximal tracheal lesions, the endoscopic findings of airway narrowing may not be the only cause of airway obstruction when mobility of the vocal folds is impaired. The best method to assess vocal fold mobility is with a flexible video-scope in an awake and cooperative patient. It is our preference to perform a flexible fiberoptic evaluation of the airway before a therapeutic intervention is undertaken. However, in cases of severe airway obstruction with impending respiratory failure, radiographic studies, FVLs and diagnostic flexible endoscopy may not be feasible and a rigid bronchoscopy should be considered in an urgent fashion to establish a patent airway.

The goals of diagnostic endoscopy are two-fold: first, to gain as much information about the airway as possible and document pertinent findings with video or still photographs, and second, to avoid precipitating an airway crisis. Once the lesion has

been evaluated endoscopically, the physician may then synthesize all of the data concerning the airway obstruction, including the history and physical and diagnostic testing, in order to plan the ideal approach to reversing the obstruction.

Management

As discussed previously, patients with central airway obstruction may present with an acute or chronic obstruction. The details of each individual case will influence how it is managed, along with the availability of medical technologies and physician expertise in a particular institution. However, it is useful to think of management strategies as being either initial stabilization or airway interventions.

Initial stabilization

The first priority of therapy must be to maintain adequate oxygenation and ventilation. Patients with a more chronic presentation might be managed with supplemental oxygen, bronchodilators and anxiolysis. Individuals with more acute presentations may require intubation and mechanical ventilation. Intubation should be attempted with anesthesia of the mucous membranes and sedation, without the use of paralysis, in order to maintain spontaneous respiration in the event that intubation is difficult. A trial of Heliox may be employed in patients with acute central airway obstruction in order to avoid intubation and to allow time for other measures (steroids, bronchodilators, racemic epinephrine) to take effect. Heliox reduces the turbulent flow of gases in large airways and may significantly reduce the work of breathing for patients with impending respiratory embarrassment [14]. Patients should be moved to an intensive care unit and preparations should be made to obtain an airway urgently, if required. The physician should study the anatomical landmarks in the neck in the event that an urgent cricothyroidotomy or tracheotomy must be performed.

Once initial stabilization has taken place, the physician is free to review the history and physical, diagnostic tests and radiographs performed to date, and order any additional studies that may prove useful. A tentative plan for intervention should be formulated at the end of this phase.

Airway interventions

Airway interventions may be categorized as endoscopic or surgical. While endoscopic interventions are generally associated with less risk, discomfort and morbidity than surgical interventions, surgery may be the definitive treatment in some cases and should be performed promptly when indicated.

Rigid bronchoscopy

Rigid bronchoscopy is a safe and effective means of establishing an airway in patients with central airway obstruction [15–17]. The rigid bronchoscope allows for ventilation, oxygenation, photographic documentation of airway pathology, control of bleeding, removal of foreign bodies and interventions ranging from balloon dilation to laser therapy. While some experts advocate the use of flexible bronchoscopic techniques in treating central airway obstruction, the rigid bronchoscope is the instrument of choice when dealing with a crisis of the central airways [18]. When dilation or recanalization of a large airway is indicated, rigid bronchoscopes with progressively larger diameters may be passed until a satisfactory lumen is obtained. This technique is generally reserved for patients with an acute presentation of airway obstruction when rapid reestablishment of an airway is required. Care should be taken to avoid mucosal injury to the larynx and trachea as endothelial injury may lead to bacterial colonization, chronic inflammation and further airway injury. Balloon dilation of the airway may be carried out with either a rigid or flexible bronchoscope when the airway obstruction is chronic and the patient has a satisfactory ventilatory reserve [19]. Balloon bronchoplasty provides a gentler dilation and allows the operator to more easily avoid mucosal injury. Dilation may also be carried out with bougie dilators, made of either metal or soft rubber, in order to provide gentle dilation with mucosal sparing [20].

Despite the cost of anesthesia services and the operating theater, rigid bronchoscopy has been shown to decrease the cost of caring for patients with respiratory failure due to obstruction of the central airways [21].

Thermal treatment modalities

Many diverse treatment modalities have the common property of applying energy to the airway, which is translated into thermal injury and cell death. Perhaps the most commonly used is light amplification by stimulated emission of radiation (LASER). Though there are many lasers in clinical use today, the vast majority of procedures are carried out with either a carbon dioxide (CO_2) laser or a neodymium: yttrium–aluminum–garnet (Nd:YAG) laser. The CO_2 laser has a wavelength of 10 600 nm and a limited tissue penetration of 0.1–0.5 mm. As a result, it is an excellent cutting tool but is ineffective in coagulating vessels over 0.5 mm in diameter. The CO_2 laser is the preferred instrument of most otorhinolaryngologists because of its utility in the larynx and subglottis. The Nd:YAG laser has a wavelength of 1060 nm and has less of an affinity for water than does the CO_2 laser. These properties allow the Nd:YAG laser to achieve tissue penetration up to 5 mm, making it an excellent tool for coagulation, but a more imprecise cutting instrument [22]. The Nd:YAG laser is readily conducted down a flexible fiber that can be passed down a bronchoscope. Therefore, most pulmonologists prefer the Nd:YAG laser for work in the trachea and mainstem bronchi. Many investigators have reported successful management of malignant and benign tracheobronchial lesions with laser therapy [23–26].

The argon plasma laser, with a wavelength of 514 nm, delivers blue–green light to the airway through a flexible monofilament. The laser energy is well absorbed by hemoglobin and water, so tissue penetration is minimal [27]. This is an excellent tool for photocoagulation. Newer delivery systems have regenerated an interest in the argon laser. Electrocautery is a technique in which an electrical current is delivered to the airway which induces heat, thermal injury and cell death. Electrocautery is an effective means of debulking benign or malignant obstructing lesions of the airway, and has the advantage of being amenable to flexible bronchoscopic techniques [28].

In contrast to all of the earlier-mentioned techniques, cryotherapy is a technique that involves the application of a hypothermic liquid nitrogen probe to the airway, resulting in cellular crystallization, edema and thrombosis of surrounding small vessels [29]. These effects take place more slowly than the other thermal modalities, making cryotherapy inappropriate if rapid debulking and recanalization of the airway is necessary. Proponents of cryotherapy argue that the technique is cost-effective, can be mastered by flexible bronchoscopists and has a lower risk of airway perforation than laser treatments [30].

Photodynamic therapy (PDT) is a technique designed to treat bronchogenic carcinoma and other endoluminal tumors of the lung in which the patient receives an infusion of a photosensitizing drug followed by flexible bronchoscopic application of laser energy with a wavelength of 630 nm. Follow-up "toilet" bronchoscopies are necessary to debride tumor, remove retained secretions and sloughed mucosa, and assess for possible additional treatment [31]. PDT is most useful in more distal airway obstruction without extrinsic airway compression. Patients with tracheal or main-stem obstruction are more readily managed with rigid bronchoscopy with possible laser assistance.

Brachytherapy

Endobronchial brachytherapy is a method of treating obstructing carcinoma in which radiation therapy is delivered internally to the airway with a bronchoscopically implanted device. It is a highly effective technique of palliating dyspnea, cough and hemoptysis [32]. The treatment may be given as an outpatient and the implanted device, usually a catheter, may be removed without the bronchoscope. There is accumulating data regarding the utility of combined Nd:YAG laser and brachytherapy for the treatment of obstructing carcinoma. Investigators have reported that follow-up brachytherapy prolongs the symptom-free period a patient achieves after rigid bronchoscopy and laser treatment [33].

Stents

Stenting of the central airways is a highly effective method of controlling endoluminal obstruction as well as extrinsic compression of the central airways [34]. In 1965, Montgomery first reported successful employment of silicone stents in the airway with his introduction of the T-tube stent for laryngotracheal stenosis [35]. Subsequently, in a seminal paper published in 1990, Dumon described his

experience with a dedicated silicone tracheobronchial stent [36]. There has been a plethora of reports in the medical literature describing successful management of airway obstruction with tracheal and bronchial stenting [37]. There are a wide variety of stent designs, but most are constructed primarily of metal or silicone. Though there is much controversy in the literature regarding the "ideal" stent [38,39], we believe that metal stents are most useful for palliation of malignant disease. Metal stents are more prone to granulation tissue formation and airway injury over time, which is less of a concern when the physician is only attempting to palliate the patient. Silicone stents are more suited for benign conditions since they may be easily removed and are associated with a lower incidence of granulation tissue formation and airway injury. They are associated with a higher incidence of mucous retention and require the use of a rigid bronchoscope for insertion. Metal stents may be inserted with a flexible bronchoscope. An experienced flexible bronchoscopist can readily master the technique. Manufacturers of metal stents do not recommend that they be removed bronchoscopically once inserted, but we have removed many metal stents with a rigid bronchoscope due to stent malfunction, reobstruction of the airway or granulation tissue formation. An exciting development in recent years has been "hybrid" stents, which are constructed of metal and silicone. These stents seem to combine the best features of both and are currently under investigation.

Surgical repair

Open surgical repair of central airway obstruction is indicated when the physiology is not appropriate for endoscopic treatment (short segment of tracheomalacia after prolonged intubation) or when endoscopic treatments have failed [40]. Surgical treatments are designed to either augment the existing airway diameter or resect the stenotic segment. Augmentation procedures focus on avoiding attempts at resecting tissue in order to preserve an intact airway epithelium in the diseased segment. Subglottic tracheal stenosis is often treated with airway augmentation. The most commonly performed augmentation procedure is laryngotracheoplasty, in which the thyroid and cricoid cartilages are split vertically and a cartilage graft is sewn into place anteriorly [41]. A laryngeal stent may be placed temporarily, at the discretion of the operator. Tracheal reconstruction and reanastamosis is done for large areas (>1 cm) of airway obstruction. Investigators have reported that 5 cm or more of the adult trachea may be resected, if necessary [42].

Some investigators feel that the enthusiasm for endoscopic treatment modalities has lead to inappropriate delay of definitive surgery for patients with laryngotracheal obstruction [43]. Thermal therapies and stenting, in inexperienced hands, may lead to further airway injury and a failure to control airway obstruction. This may not only delay definitive surgical treatment, but also make surgery more technically challenging.

Conclusions

Obstruction of the central airways may manifest in a wide variety of presentations from simple exertional dyspnea to an acute airway crisis. Evaluation should focus on a careful history and physical, appropriate radiographic studies, and a review of old medical records. Treatment must be aimed at initial stabilization, followed by airway intervention that has been carefully planned. A multidisciplinary approach, employing the expertise of interventional pulmonologists, otolaryngologists and thoracic surgeons is ideal.

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CHAPTER 23

Management of massive hemoptysis

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Introduction

A widely accepted definition of hemoptysis is bleeding emanating from below the glottis. It is a common problem presenting to a variety of clinical practices. Hemoptysis represents 6.8% of chest clinic visits and 11% of thoracic surgical admissions, and may be life threatening requiring intensive management [1]. A survey performed at the American College of Chest Physicians (ACCP) in 1988 revealed that hemoptysis was the second most common indication for bronchoscopy in chest physicians' practices [2]. The diagnostic and therapeutic management of hemoptysis has changed over the years secondary to changing etiologies and improvements in endoscopic and vascular therapeutic modalities. In this chapter we will focus primarily on massive hemoptysis, reviewing the definition, vascular anatomy, differential diagnosis and current diagnostic and therapeutic approaches based on available data.

Definitions

There are two major approaches to defining massive hemoptysis. The first consists of volumetric definitions and the second relates to the magnitude of its effect. The volumetric definition specifically describes a quantity of blood expectorated in a period of time. It has traditionally been used to grade the severity of the hemoptysis. Although no strict definition exists regarding massive and nonmassive volumes, the consensus is that less than 100 mL in a 24-h period represents nonmassive hemoptysis [3]. The volume criteria cited for massive hemoptysis range from 100 to 1000 mL in a 24-h period.

Perhaps the most widely referenced volume criterion for massive hemoptysis parameter has been documentation of 600 mL of bleeding in 24 h. Crocco *et al.* looked at the rate of bleeding in 67 patients with hemoptysis [4]. Those who expectorated 600 mL in less than 4 h had a mortality of 71%; 600 mL in 4–6 h had 45% mortality whereas those who expectorated this amount in 24–48 h had less than 5% mortality.

The magnitude of effect definition implies that the consequences of the expectorated blood are more important than the absolute volume. Hemoptysis is often difficult to accurately quantify at the bedside. If the hemoptysis results in alterations in hemodynamics, gas exchange and puts the patient at large risk for clot aspiration it is classified as massive. Further delineation involves abnormalities in laboratory values requiring blood product transfusion [5]. The definition for asphyxiating hemoptysis requires bleeding rates in excess of 150 mL/h, potentially causing airway occlusion and hypotension from volume loss [6]. 'This definition is based upon the average anatomic dead space of the tracheobronchial tree in an adult measuring approximately 150 cc.

Vascular supply

Familiarity with the vascular supply, drainage and anastomotic sites of the pulmonary circulation is

necessary in order to understand the etiology of hemoptysis. Most causes of hemoptysis originate from the bronchial systemic circulation. The bronchial arteries are branches of the aorta or its tributaries and supply the proximal airways to the level of the terminal bronchioles. They also supply mediastinal, hilar and visceral pleural structures. Distal supply to the alveolar sacs and ducts is accomplished via a diffusion gradient through the pulmonary circulation and capillary bed [7].

The bronchial circulation represents about 2% of the left ventricular output and is exposed to systemic pressures. The venous drainage system includes the azygous system and the pulmonary veins. Anastomotic connections that exist between bronchial and pulmonary capillary beds contribute to the normal right to left shunt.

Substantial evidence exists that bronchial arteries are the most common source of hemoptysis. Angiographic studies illustrate bronchial artery dilation, ectasia and collateral formation usually coinciding with the localized site of bleeding. On occasion the bleeding bronchial artery can be seen during angiography. Also vascular embolization of these vessels typically results in cessation of bleeding. There are, however, occasions where the pulmonary circulation is the culprit. Rupture secondary to pulmonary artery catheter inflation, pulmonary aneurysms secondary to connective tissue disorders and vasculitis are such examples.

Table 23.1 The differential diagnosis of hemoptysis.

Infectious	Tuberculosis (primary or reactive)
	Bacterial
	Fungal
	Viral
	Parasitic
	Abscess formation
	Bronchiectasis
Neoplastic	Primary bronchogenic
	Metastatic disease
	Endobronchial extension
Systemic	Goodpasture's
	Wegener's vasculitis
	Collagen vascular disease
	Sarcoidosis
	Idiopathic pulmonary hemosiderosis
Occupational	Trimellitic anhydride
	Occupational solvents
Pharmacologic	Over-the-counter (Aspirin)
	Prescription drugs (Coumadin)
	Cocaine
Trauma	Bronchial fracture
	Pulmonary contusion
	Vascular injury
Hematologic	Coagulopathy
	Thrombocytopenia
	Marrow suppression
	Disseminated intravascular coagulation
Cardiac disease	Valvular heart disease
	Cardiac defects
	Aorto-bronchial fistula

Differential diagnosis

The differential diagnosis of hemoptysis has changed over the years secondary to improved prevention and treatment strategies for tuberculosis. It includes infectious etiologies, bronchiectasis, malignancy, pulmonary abscess, foreign body aspiration, mycetomas, valvular lesions, vascular aneurysms, aortic communication, vasculitis, drug–induced baseout, occupational diseases, coagulopathies, iatrogenic and miscellaneous etiologies. Although a detailed description of all causes is beyond the scope of this chapter, a few specific disease entities will be covered (Table 23.1).

Tuberculosis in older studies accounted for 73% of all causes of hemoptysis [4]. This included both new and inactive cases. The study by Conlan *et al.* in 1983 showed that tuberculosis was the cause in only 38% and that bronchiectasis accounted for 30% [8] of all patients with hemoptysis. The potential reason for this decrease in incidence may relate to improved prevention, prophylaxis and chemotherapeutic strategies. Tuberculosis may cause hemoptysis via a variety of pathophysiologies: (a) direct extension of tuberculous infection and inflammation into bronchial arterioles may result in bleeding; (b) bronchiectasis from chronic infection, obstruction and parenchymal destruction may result in large, tortuous, fragile bronchial arteries, which may bleed spontaneously; (c) large parenchymal cavities may be secondarily infected with mycetomas resulting in friable granulation tissue and neovascularization (Rasmussen's aneurysm); and (d) pulmonary artery invasion,

dilation and rupture may occur as a consequence of tuberculous infection.

Bronchiectasis results typically from chronic obstruction and infection of a segmental bronchus. It may complicate congenital disease processes such as cystic fibrosis and dysmotile cilia syndromes along with a host of acquired diseases such as infections and pulmonary pathologies. Although different etiologies account for this, the end pathophysiology is the same. The bronchial arteries become enlarged, dilated, ectatic and usually form extensive collateral vessels. These large vessels are prone to spontaneous rupture and may result in aggressive hemorrhage.

Pulmonary malignancies, either primary bronchogenic or metastatic, may result in endobronchial involvement. Data from the American Cancer Society showed that only 15% of all lung cancer patients are resectable. Up to 80% will develop malignant tracheobronchial involvement at some point in their disease process [9]. These lesions are typically vascular, may obstruct the airways distal to the tumor and bleed spontaneously.

Mycetomas, typically aspergillus, may secondarily infect cavitary lung disease. They cause large bronchial artery dilations and invade the vascular intima. Often these can be easily diagnosed by decubitus chest radiographs, or computed tomography (CT) scans revealing positional changes in the lesion or a crescent sign in the cavity.

Lastly, post-obstructive lung abscesses are a relatively common cause of hemoptysis. Hemoptysis may result directly from airway obstruction secondary to foreign body aspiration, benign cysts and tumors, tracheobronchial extension of malignancies or anatomically distorted airways. The parenchymal destruction that results may involve both the bronchial and pulmonary circulation and lead to significant hemoptysis.

Diagnostic evaluation

The diagnosis of hemoptysis can be challenging. Although the expectoration of blood seems clinically easy to diagnose, several other disease processes may result in coughing up blood. Aggressive sinus and posterior nasal bleeds typically result in aspiration of blood into the airway and resultant "pseudohemoptysis." This may confuse the clinical picture since the patient will present with apparent hemoptysis and an abnormal chest radiogram. Also aggressive bleeding from the gastrointestinal tract may cause cough from aspiration or blood in the esophagus.

Table 23.2 Historical clues used for the differentiation of hemoptysis from an extra-pulmonary source of bleeding.

	Hemoptysis	*Extra-pulmonary etiology*
Symptoms	Chest	GI, epistaxis, sinusitis
Cough/Vomit	Coughed	Vomited
Color	Bright red	Dark
Sputum texture	Frothy	Particulate matter
Oxygen content	SaO_2	SvO_2
PH	Alkaline	Acidic

Historical clues regarding the nature of the sputum may help differentiate true hemoptysis from "pseudohemoptysis." Bright, red, frothy sputum with an alkaline pH implies a systemic, oxygenated bronchial arterial source of bleeding. A history of hematemesis, nausea and vomiting, dark sputum with food particles, poorly saturated hemoptysis with a low pH implies a gastrointestinal source (Table 23.2). Patients with true hemoptysis are usually able to localize the source of bleeding to a specific lung or segment. Vague sensations of pressure, tightness, gurgling and secretion accumulations are all well described. Some of these sensations, however, may be reproduced by a rapid upper gastrointestinal bleed or a brisk posterior nasal bleed. Often a multidisciplinary diagnostic approach is needed to identify the true source of bleeding.

Once the diagnosis of hemoptysis is made a complete history and physical along with simultaneous laboratory and radiologic evaluation is required. Although it is beyond the scope of this chapter to review all historical data, pertinent clues will be reviewed.

The patient's age is important in narrowing the differential diagnosis. Bronchiectasis or valvular lesions typically cause hemoptysis in patients less than 40 years of age. In those patients over 40 with a history of cigarette smoking, the etiology of the hemoptysis is more likely to be caused by bronchogenic neoplasms. Previous history of tuberculosis exposure, infection and prior PPD status are

important given the high incidence of hemoptysis complicating tuberculosis. Chronic and recurrent episodes of pneumonia may lead to the diagnosis of acquired or congenital bronchiectasis. A complete drug history including prescription drugs, over-the-counter medication and illicit drug use is important in narrowing the differential diagnosis. Finally, a detailed occupational history is important, as hemoptysis may be a sequela of certain toxic exposures.

A specifically tailored physical exam may also provide clues toward the etiology of the hemoptysis. The presence of clubbing, adenopathy and localized wheezing may represent underlying malignancy. Valvular lesions can typically be auscultated. Nasal septal ulcerations or cartilaginous deformity may suggest to the practitioner a diagnosis of Wegener's granulomatosis. Mucocutaneous telangiectasias may point to a diagnosis of Osler–Weber–Rendu syndrome. The presence of petechiae may suggest an underlying coagulopathy.

Initial laboratory evaluation should include a hemoglobin and hematocrit with serial follow-up to assess the magnitude of the effect of the hemoptysis. Platelet counts and coagulation profiles are important to initially assess and follow since coagulopathy may cause or result from significant hemoptysis. Serological markers, including antinuclear antibodies, rheumatoid factor and other connective tissue serology should be drawn. It is also important to obtain blood for anti-basement membrane (anti-GBM) antibodies (Goodpasture's) and anti-neutrophil cytoplasmic antibodies (ANCA-Wegener's), but these are rarely helpful in the immediate clinical setting. Simple urinalysis may be useful in diagnosing a pulmonary–renal syndrome by detection of an active urinary sediment containing red cell casts. Finally, sputum analysis with gram, AFB and fungal stains, as well as culture can be helpful in diagnosing pulmonary infections that may be causing hemoptysis.

Chest radiographs

Chest radiographs are important initial tests for both the diagnosis and lateralization of the source of bleeding. Specific disease entities such as malignancies, tuberculosis, mycetomas, bronchiectasis and lung abscesses may be strongly suspected from the radiograph. Chest radiographs are an important tool in localizing the area of bleeding to help direct bronchial artery embolization (BAE). Commonly these vessels are not actively bleeding during the time of angiography and knowledge of the bleeding focus is essential. In a study performed by Haponik *et al.* the chest radiograph was able to localize the bleeding site in 65.4% of the patients [10].

There are however, limitations to the utility of the chest radiograph. Often the focus of bleeding spills over to the contralateral lung giving a vague alveolar filling process on the radiograph. Several abnormalities with different treatment algorithms may appear similar on the chest radiograph. Several causes of massive hemoptysis may be radiographically silent. Examples include bronchiectasis, endobronchial malignancies, carcinoid tumors, broncholiths, aorto-bronchial fistula and pulmonary embolism.

Chest computed tomogram

Some controversy persists over the utility and necessity of the chest CT in the diagnosis of both nonmassive and massive hemoptysis. Does the CT scan add to the chest radiograph? In the Haponik study the CT scan provided new diagnostic information in 46.9% and clarified abnormalities in an additional 15.6% [10]. It was also able to successfully localize the source of bleeding in 88.5% of the patients. Several studies have looked at the utility of CT scanning in normal or nonlocalizing chest radiographs. Miller *et al.* showed that CT scans were able to localize the abnormality in 50% of these patients [11]. Magu *et al.* studied 30 patients with a normal chest radiograph and hemoptysis [12]. They found diagnostic information from the CT scan in 53% of the patients.

Does the CT scan offer additional information not gained by early bronchoscopy? Set *et al.* looked at 91 patients with hemoptysis, and compared CT scanning with bronchoscopy for the diagnosis of lung cancer [13]. CT demonstrated all 27 tumors seen at bronchoscopy and an additional 7 not seen endoscopically. CT was insensitive for demonstrating mucosal abnormalities such as bronchitis, metaplasia and papillomas. The author concluded

that bronchoscopy should be the first examination performed. CT scanning should be reserved for a non-diagnostic bronchoscopy and strong clinical suspicion for malignancy. Haponik studied 32 patients with hemoptysis to elucidate the roles of CT and bronchoscopy in this setting [10]. Although CT scans augmented radiographic yield above and beyond chest radiographs, performance of chest CT scans did not obviate the need for bronchoscopy. The CT influenced the management in 6 patients, added to the combined yield of bronchoscopy and chest radiograph in only 2, and changed the management in only 1 patient. The authors did not recommend the widespread routine use of CT scans.

McGuinness *et al.* studied 57 patients with hemoptysis [14]. The etiology of the hemoptysis was bronchiectasis (25%), tuberculosis (16%), lung cancer (12%), aspergilloma (12%) and bronchitis (12%). They found CT scanning and bronchoscopy to be complimentary. The CT scan was useful in diagnosing bronchiectasis and, aspergillomas and bronchoscopy was helpful in diagnosing mucosal lesions and bronchitis. Flexible bronchoscopy in their study localized the bleeding in only 51% of the patients, making the CT a necessary adjunct to diagnosis and management.

Diagnostic bronchoscopy

Should bronchoscopy be performed routinely in patients with hemoptysis? Several large studies looked at the utility of bronchoscopy in hemoptysis with a normal or non-localizing chest radiograph. Poe *et al.* studied 196 patients and found a 6% incidence of bronchogenic carcinoma and a 17% incidence of other pathology diagnosed at bronchoscopy [15]. Lee *et al.*'s retrospective chart review of 478 patients with hemoptysis and a normal chest radiograph reported only a 2.1% incidence of malignancy and an overall diagnostic yield of 4.2% [16]. O'Neil *et al.* looked at 119 patients and found a 5% incidence of neoplasm diagnosed at bronchoscopy [17].

Although the reports mentioned earlier suggest a low diagnostic yield for bronchoscopy, there are specific factors that improve the yield in this patient population. The presence of smoking in excess of 40-pack-years, age greater than 50, male sex and hemoptysis greater than 30 mL in a 24-h period greatly improved the yield. In the Poe study, the presence of two of these factors with hemoptysis greater than 30 mL per 24 h correlated with malignancy in 100% of the patients and increased the overall diagnostic yield to 82%.

Given this data, it is recommended that chest radiographs be performed in all patients with hemoptysis. It is an inexpensive test with great utility in diagnostic and therapeutic algorithms. The widespread use of CT scanning however is neither cost-effective nor indicated. It rarely changes the management in patients with a localizing chest radiograph and diagnostic bronchoscopy. It should be reserved in those cases where chest radiograph and bronchoscopy did not diagnose or localize the pathology. Early bronchoscopy is supported in those cases where risk factors previously detailed are present and hemoptysis is greater than 30 mL in a 24-h period. It is indicated for massive hemoptysis as a localizing strategy for definitive therapy and possibly for endoscopic therapeutics.

Management

It is artificial to outline a stepwise approach for the management of patients with massive hemoptysis since most of these interventions are performed simultaneously. It is prudent, however, to start with airway stabilizing techniques while diagnostic evaluation and definitive therapeutics are being pursued. The decision to intubate a patient with hemoptysis is always a clinical one and difficult to delineate. Clearly, inability to clear secretions, aspiration of clot with airway occlusion, hemodynamic instability and the inability to oxygenate and ventilate all require urgent intervention.

Airway stabilization

Airway stabilization in focal hemoptysis ultimately relies on the ability of the physician to intubate, protect the "good lung," isolate the bleeding lung and tamponade the source of bleeding. The airway techniques can be grouped into four major strategies: a single lumen endotracheal tube directed into the good lung; a single lumen tube with a balloon blocker; a single lumen tube and then a bronchoscopically placed balloon catheter

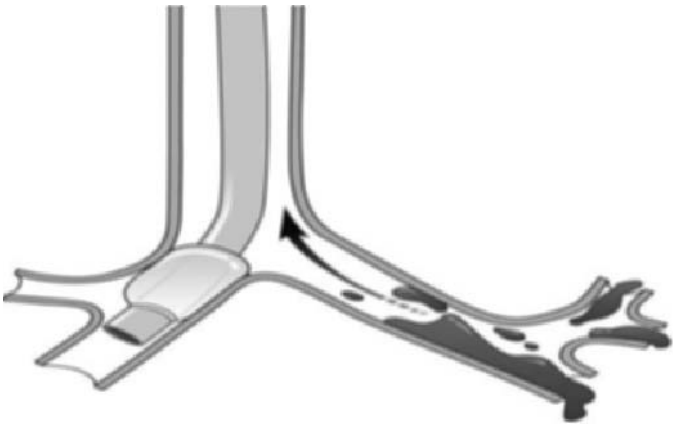

Figure 23.1 This figure illustrates selective intubation of the right mainstem bronchus.

in the bleeding lung; or a double lumen endotracheal tube.

Endotracheal tube placement directed specifically to the good lung may be performed at the bedside (Figure 23.1). This assumes that the bleeding source has been localized. The technique differs depending on the lung to be selectively intubated. Selective intubation of the right lung is accomplished by slow advancement of the tube while auscultating both lungs. The straighter angulation of the right mainstem bronchus will direct most tube advancements to this location. The exact distance to advance can be gauged by when the auscultated breath sounds in the left lung diminish. Inflation of the balloon may help prevent major contralateral clot aspiration.

Selective left lung intubation is more difficult. There are specifically designed endotracheal tubes for this purpose that have a left angulation and are less compliant to help facilitate turning in the trachea. The vocal chords are visualized using standard laryngoscopic techniques, the tube is advanced past the chords with the angle facing anterior and parallel to the chords. Midway through the trachea the tube is rotated 90° to the left and advanced until breath sounds in the right lung diminish. The cuff is then inflated. This technique is more difficult since standard endotracheal tubes may not turn smoothly in the trachea and may require bronchoscopic repositioning.

The Inoue endotracheal tube has a self-contained balloon catheter that can be advanced into a specific lung (Figure 23.2). These tubes are routinely used for single lung ventilation and lung collapse during thoracic surgery or thoracoscopy. The balloon catheter can be blindly or endoscopically advanced into the appropriate mainstem bronchus after intubation. This serves to isolate the bleeding lung and the blood can be aspirated.

The endoscopic deployment of a balloon catheter is another option to the bronchoscopist. Usually this is performed through an endotracheal tube. The site of bleeding is visually identified via bronchoscopy. A balloon catheter can then be passed through the working channel of a flexible bronchoscope and inserted into the appropriate segment of lung. The bronchoscope is then backed out of the airway, leaving the balloon in place, which is then inflated to occlude the segment. If the balloon required is too large for the flexible bronchoscope working channel, it can be inserted either through a rigid bronchoscope, by using a guidewire fluoroscopic technique, or through the endotracheal tube using the replacement technique detailed later.

The guidewire technique requires fluoroscopy for placement of the balloon catheter. The bronchoscope is used to identify the bleeding lung and segment. Radiopaque markers are placed on the chest corresponding to the segment of lung to be blocked. A guidewire is placed through the side channel of the bronchoscope and directed to the segment. The bronchoscope is then removed leaving the guidewire in place. The balloon is placed over the guidewire and advanced until its proximal and distal markers line up with

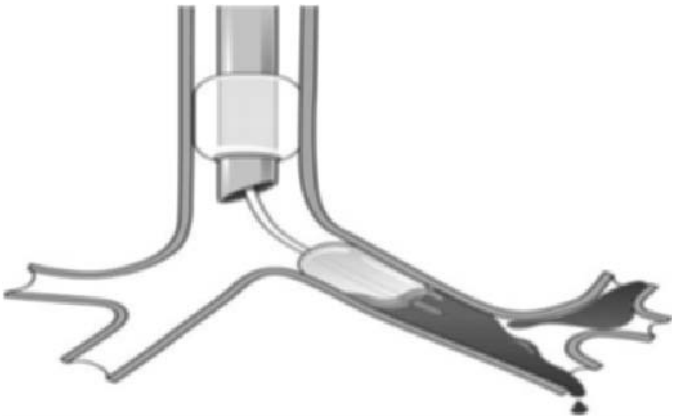

Figure 23.2 An endotracheal tube with self-contained balloon blocker is shown.

the chest markers. The balloon is inflated to the appropriate number of atmospheres, measured with an interposed manometer and left in place. Disadvantages of this technique are that it requires the proper equipment and time for set-up (Figure 23.3a–d).

Alternatively, the bronchoscope can be used to advance the endotracheal tube into the appropriate lung. The bronchoscope is removed and the balloon catheter is placed through the endotracheal tube into the lung segment. The endotracheal tube is slowly withdrawn back to the level of the carina (Figure 23.4a–d). The balloon catheter is inflated and occludes the mainstem. Most balloons have a central lumen allowing for the withdrawal and accurate measurement of the hemoptysis.

Finally, a double lumen endotracheal tube may be inserted. The original Carlens tube sits on the carina and has a tracheal and left mainstem balloon. The modified Robertshaw tube lacks the carinal hook of the Carlens tube, and has a larger lumen size that allows passage of a flexible bronchoscope [18] (Figure 23.5). The double lumen tubes are available in both right and left lung varieties. The left, however, is more commonly used, secondary to the relatively short length of the right mainstem bronchus preceding the takeoff of the right upper lobe bronchus. The double lumen tube is placed into the trachea and the bronchoscope is inserted through the endotracheal tube into the left mainstem lumen. The tube is passed over the bronchoscope into the left mainstem bronchus, the bronchoscope is pulled back to the carina and the left mainstem balloon is inflated under bronchoscopic visualization.

Standard resuscitative techniques are performed during the initial assessment. Fluid resuscitation, pressor medications and blood products are given as indicated. Appropriate laboratory and serologic studies are performed. Disease specific therapies are considered such as immunosuppressive therapy for vasculitis, connective tissue disorders and Wegener's granulomatosis. Corticosteroids and plasmapheresis may be useful in the setting of Goodpasture's. In the setting of massive hemoptysis from a focal source, always obtain early thoracic surgical consultation, in case urgent surgical lung resection should prove necessary.

As a temporizing measure, the patient is placed in the lateral recumbent position with the bleeding lung down. Although there have been no studies demonstrating a survival advantage with this technique, it certainly makes intuitive sense. Most of the difficulty in managing these patients is due to clot formation and airway occlusion. Keeping the bleeding lung in a dependent position may help prevent contralateral spill over and airway occlusion, although it may also theoretically potentiate hemoptysis by increasing gravitational blood flow to the site of bleeding.

Pharmacological agents have been used to decrease bronchial blood flow by increasing bronchial vascular resistance. Long *et al.* looked at aerosolized histamine in intubated sheep and measured bronchial artery blood flow [19]. This resulted

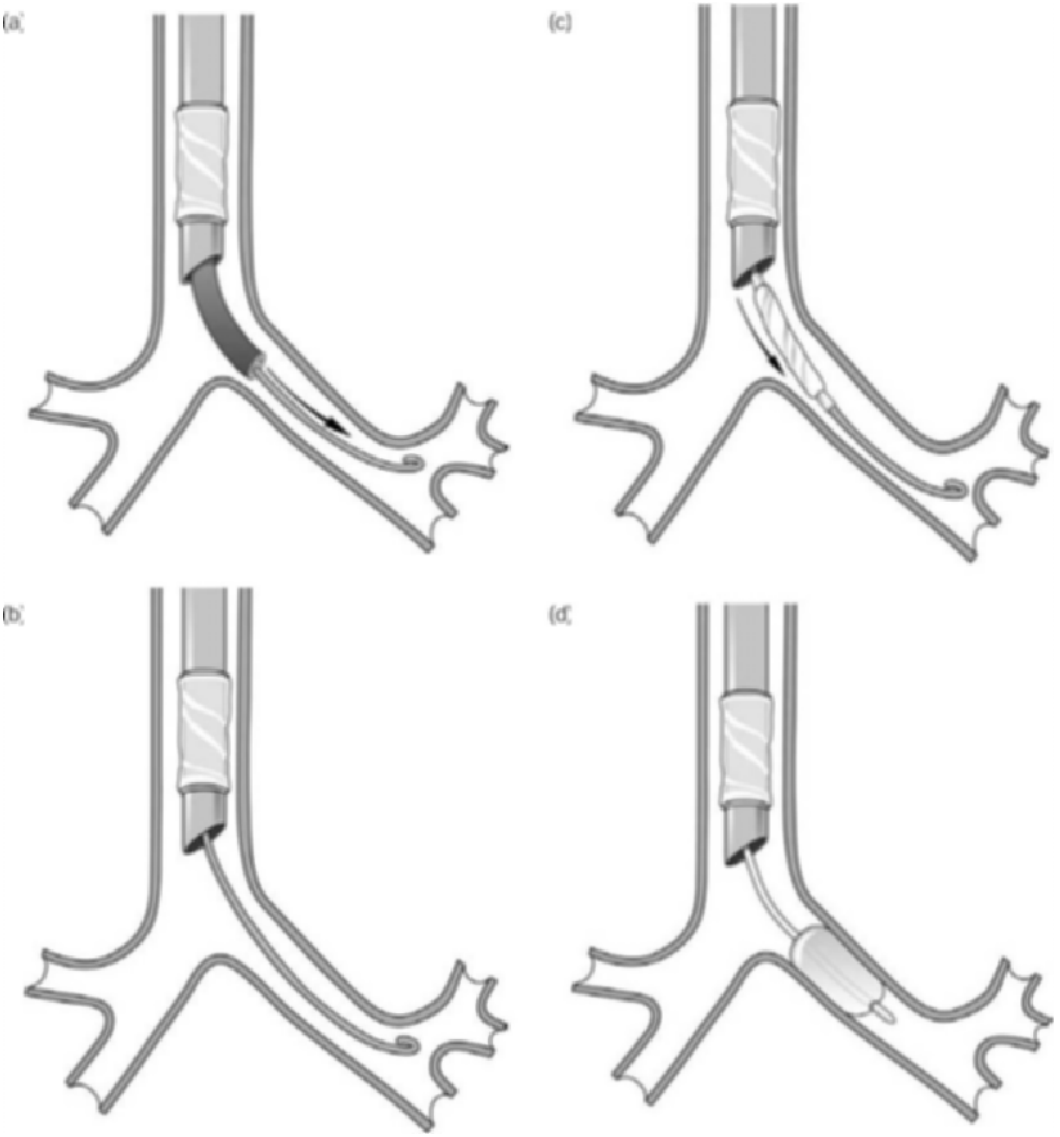

Figure 23.3 (a—d) The bronchoscopic placement of a balloon catheter using a guidewire replacement technique is illustrated (see text).

in a 53% increase in blood flow, which was prevented by pretreatment with chlorpheniramine. This has lead to anecdotal reports of the use of intravenous cimetidine 200 mg every 8 h as a stabilizer for hemoptysis. Indomethacin, a nonspecific cyclooxygenase (COX) inhibitor has also been tried experimentally, despite its potential inhibitory effects upon platelet function. No controlled studies support the use of these medications in hemoptysis.

Several studies have looked at the use of vasopressin in the treatment of massive hemoptysis [20,21]. Most of the studies included small numbers of patients with a reported diminished bleeding rate. Since hemoptysis tends to be episodic it is difficult to show a direct effect from the vasopressin. Multiple other modalities were used to decrease the bleeding and this confounds the interpretation of these studies. The use of vasopressin was not randomized and poorly controlled.

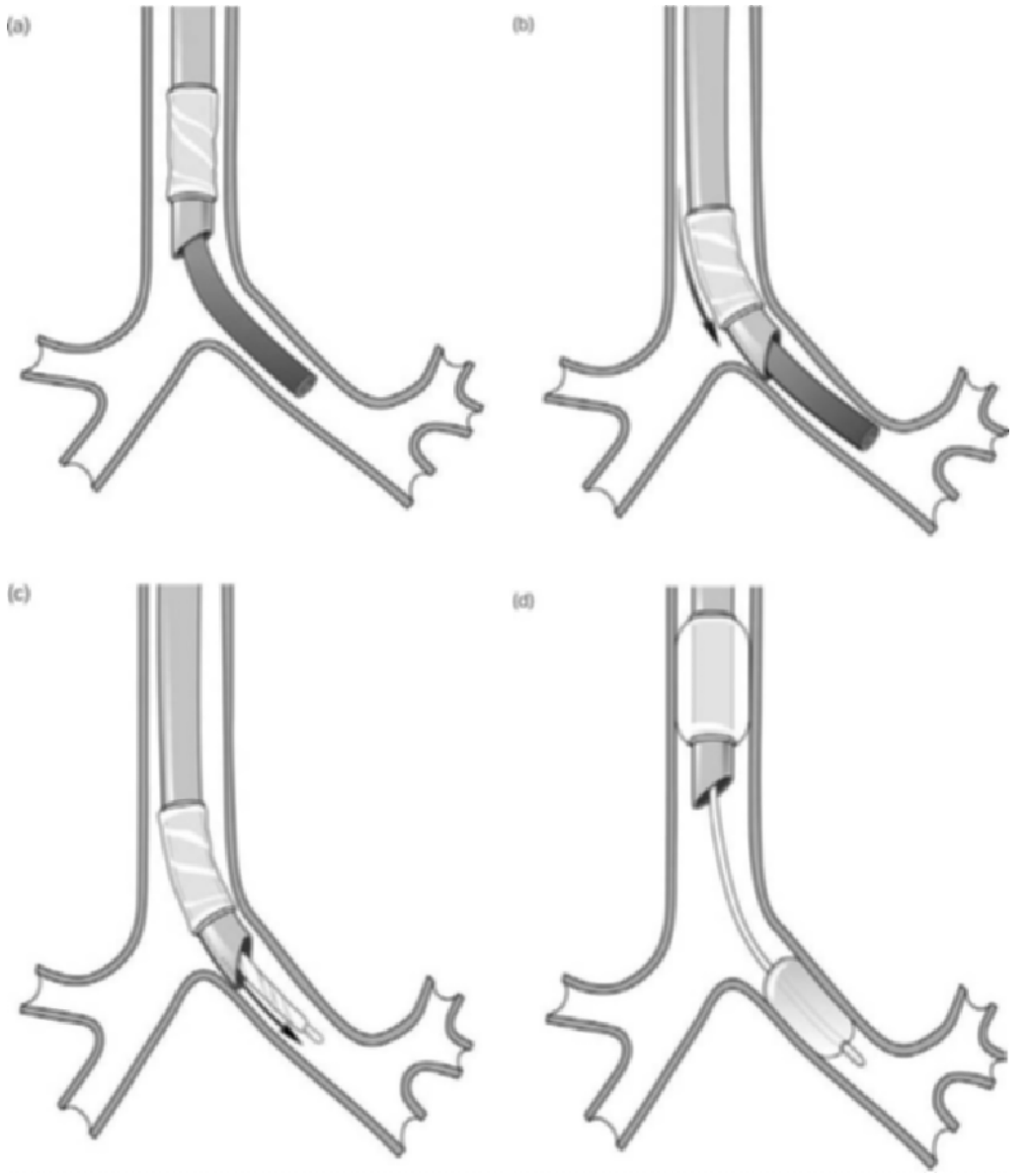

Figure 23.4 (a–d) An alternative method for placement of the balloon catheter when it is too large to fit down the side channel of the bronchoscope is illustrated (see text).

Insufficient data exists to recommend the use of vasopressin in this setting.

Endoscopic therapeutics

Bronchoscopy is an important tool for the evaluation and management of these patients. It is adjunctive for airway control, secretion clearance, bleeding localization and endoscopic therapeutic intervention. Whether to use a rigid or a flexible bronchoscope is commonly debated, but has never been studied in a controlled randomized fashion. A recent ACCP survey revealed that fewer than 8% of pulmonologists perform rigid bronchoscopy [2]. With the advent of double lumen and Inoue

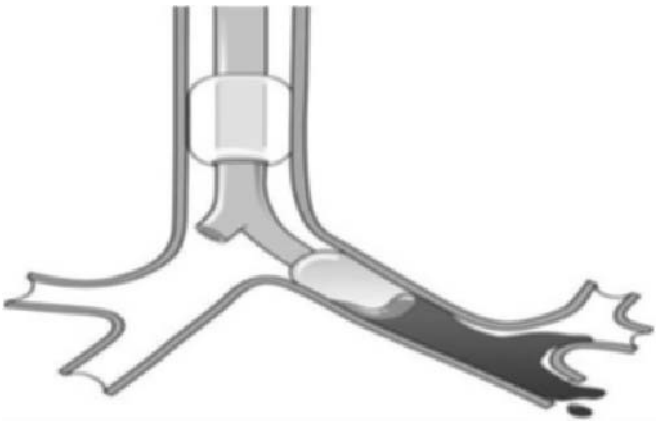

Figure 23.5 A Robertshaw double lumen endotracheal tube is illustrated with both balloons inflated.

endotracheal tubes, a decreasing number of surgeons are routinely performing rigid bronchoscopy. There are advantages and disadvantages to both flexible and rigid bronchoscopic techniques.

The rigid bronchoscope has an assortment of tracheal and bronchial ventilating barrels, which allow for airway control and contralateral lung ventilation. A suctioning and therapeutic attachment facilitates secretion removal and the passage of a laser fiber. An important component is the ventilating side port allowing for the administration of general anesthesia. The light source and telescope allow for both direct and video-assisted visualization.

Rigid bronchoscopy usually requires general anesthesia and in most facilities is performed in an operating suite. Because of the large barrel size all therapeutic techniques may be easily performed. It accommodates a laser, large cryotherapy probes, electrocautery probes, photodynamic therapy (PDT) fibers, metallic and silastic stent placement and airway dilators. The barrel of the rigid bronchoscope itself can be used to core out tumors after the blood supply has been adequately coagulated. Rigid bronchoscopic inspection, however, is limited to the central airways. This limitation is easily overcome by placing a flexible bronchoscope through the lumen of the rigid bronchoscope for full inspection.

In contrast, flexible bronchoscopy is routinely performed by many specialties and is an integral part of all pulmonary training programs. It is easily performed at the bedside using conscious sedation. The flexibility of the bronchoscope allows for detailed distal airway inspection, and the larger therapeutic bronchoscopes will facilitate many interventions. The issue of airway control is routinely overcome by performing the procedure through the endotracheal tube. Secretion and blood clearance is not as efficient as rigid bronchoscopy and certain stents can only be deployed through a rigid system. Clearly, the choice of bronchoscope is a matter of personal preference, training and equipment availability at the local facility.

Topical agents

Endoscopically applied topical agents have been used to control the bleeding source in the airway. These can be broadly classified into vasoconstrictive and procoagulant agents. The therapeutic application of cold water has been used as a gastric coagulant; cold saline lavage in the airways has also been used to control bleeding. The proposed mechanism of action is hypothermia-induced vasoconstriction. There have been anecdotal reports of its success. One such case series reported by Conlin and Hurwitz described the use of iced saline lavage in 12 patients with massive hemoptysis [22]. Rigid bronchoscopy was performed and the bleeding site was lavaged with 50 mL cold saline aliquots until hemorrhage ceased. The average volume of cold saline required was 500 mL; five patients required repeat endoscopy for recurrent bleeding. No mortalities occurred in the study.

Topical epinephrine has also been used to arrest airway bleeding. Dupree *et al.* studied 7 patients with significant hemoptysis and treated

them with topical cold epinephrine–saline solution (1 : 10 000–100 000) [23]. They had an 85.7% survival with patients requiring between 1 and 20 (!) bronchoscopic applications. Pue and Pacht, in a retrospective review of 4273 patients, documented a 2.8% bleeding complication rate as a result of transbronchial lung biopsy [24]. All episodes of bleeding in this report were successfully treated with the topical application of epinephrine.

Endoscopically applied pro-coagulants have also been used to control hemoptysis. Small studies using fibrin, fibrin precursors, fibrin – thrombin glue preparations and fibrinolytic inhibitors – have reported efficacy [25,26]. This technique usually requires double lumen catheters placed down the bronchoscopic side channel to the appropriate segment. The agents are injected into the bleeding segment and the bronchoscope is removed. Although the results have been favorable, these studies are not controlled, randomized or large enough to make any broad conclusions regarding their clinical utility.

Laser bronchoscopy

Laser bronchoscopy has been performed since 1972 by Strong and associates using the CO_2 laser [27]. With advancements in laser technology and delivery systems use of the laser became the mainstay for endoscopic coagulation. Dumon and Personne popularized the Nd: YAG (neodymium–yttrium–aluminum–garnet) laser for bronchial use [28,29]. Its wavelength of 1064 nm imparts specific laser – tissue interactions making it desirable for bronchoscopic use.

When a laser is fired upon tissue, several responses may occur: (a) no absorption resulting in reflection of the beam back to the operator; (b) 100% absorption with superficial energy dissipation; and (c) poor absorption with deeper penetration of laser energy into target tissue. As the laser energy is dispersed in the tissue, it has a specific scatter coefficient. In addition tissue pigment will affect absorption and scatter of the energy pulse. The Nd: YAG laser has a lower absorptive coefficient than scatter coefficient allowing for deeper penetration and a wide coagulation zone.

The Nd: YAG delivery fiber is small and flexible allowing for its use through both a rigid and flexible bronchoscope. The fibers are available in both noncontact and sapphire-coated contact varieties. Several safety issues surround its use. The laser may ignite flammable structures such as bronchoscopes, endotracheal tubes, suction catheters and other plastic objects. Strict adherence to a low fraction of inspired oxygen is imperative in limiting the occurrence of endobronchial fire. Viral particles may be transmitted in laser plume requiring an appropriate evacuation system. This is of particular importance in the setting of airway papillomas and patients with HIV.

The technique for performing laser bronchoscopy is straightforward. The lesion should be proximal with an endoluminal component. This will allow for a parallel aiming beam thus decreasing the incidence of airway perforation. A flexible or rigid bronchoscope is inserted. The FiO_2 is reduced to less than 40% and the fiber is inserted down the side channel. The probe is advanced to approximately 5 mm proximal to the lesion, but distal to the bronchoscope, endotracheal tube or any flammable objects. Low wattage is initially used in a pulsed fashion. Most practitioners will start at 20 W and increase based on tissue response. After the tissue has been adequately coagulated it may be debulked with a cryotherapy probe, biopsy forceps or the barrel of the rigid bronchoscope.

With appropriate training laser bronchoscopy is a safe and effective modality for coagulating tumor lesions. Cavaliere *et al.* performed 2610 laser procedures with successful airway palliation achieved in 93% of the patients [30]. The overall mortality rate was less than 0.4%. Personne *et al.* studied 1310 who patients received laser bronchoscopy [29]. The mortality rate in their group was less than 1%.

It should be clarified, however, that the role of laser photocoagulation in massive hemoptysis is limited to those patients with focal endobronchial pathologies. There is no role for bronchoscopic laser therapy in patients with hemoptysis secondary to bronchiectasis, pulmonary AVMs, etc.

Electrocautery

Electrocautery has also been used successfully in the airways to coagulate bleeding foci. New

developments in bronchoscopes with improved grounding technology have made electrocautery a safe, inexpensive alternative to laser endoscopy. Argon plasma coagulation (APC) is essentially a noncontact form of electrocautery. Several studies have looked at the safety and utility of these modalities [31,32]. For example, Morice *et al.* performed APC on 60 patients with endobronchial lesions causing hemoptysis and/or airway obstruction. This group demonstrated a 100% success rate in control of hemoptysis with APC after a mean follow-up period of 97 days [31].

Other endoscopic modalities have been used for the immediate control of hemoptysis with less success. The therapeutic application of extreme cold in the form of cryotherapy is not typically successful in halting hemoptysis from endobronchial tumor. The coagulation effects are typically delayed 24–48 h making it a suboptimal choice. PDT would also not be an appropriate choice for immediate control of bleeding. PDT requires the injection of a photoporphyrin 48 h prior to the laser application, and would therefore not be an option for immediate control of massive hemoptysis. In the future, the utilization of rapid-acting photosensitizers such as topical 5-aminolevulinic acid (5-ALA) may expedite the PDT process, facilitating its use in acute situations such as hemoptysis.

Bronchial artery embolization

Surgical intervention was the definitive therapy for those patients with significant hemoptysis prior to 1973. These surgeries including lobectomies and pneumonectomies were problematic, as many of these patients had comorbid illnesses making surgical resection high risk. Extensive lung destruction and the presence of dense pleural adhesions in some patients made lobectomy or pneumonectomy technically difficult with high complication rates. Available studies show a mortality rate ranging from 0.9 to 50% [33,34].

With the advent of BAE, treatment strategies for massive hemoptysis have changed. As previously discussed bronchial arteries are commonly the source of bleeding. Angiographically these vessels are dilated, ecstatic and often have extensive collateral formation. Rupture of these friable vessels may result in massive hemoptysis. Angiographic treatment strategies have evolved to destroy these vessels and thus halt the hemoptysis.

Embolization of these vessels may be accomplished with different agents. The angiographic placement of gelfoam, absorbable gelatin sponges, cyanoacrylates, steel coils, polyvinyl alcohol and other sclerosing agents have been used to occlude vessels in areas of localized bleeding. There have been several studies looking at the initial response and relapse rate for BAE. Cremaschi *et al.* looked at 209 patients who received BAE for various causes of hemoptysis [35]. Bronchiectasis and tuberculosis accounted for 78% of the patients. They demonstrated an initial response rate of 98% with a 16% 1-year relapse rate.

Yu-Tang *et al.* studied 134 patients treated with BAE for hemoptysis [36]. The etiology in that group was predominately tuberculosis (83.6%). On angiography the bronchial arteries were dilated in 88.3%; about one-third of these had a nonbronchial systemic contribution. This situation occurs most commonly in the setting of mycetomas with the parasitization of blood supply from the adjacent chest wall vasculature (axillary, long thoracic, internal mammary, etc.). Initial success rates for BAE in this study were 81.6% with a median 9.5-month follow-up. Of the 18.4% that failed initial BAE, 58% went on to surgery and 42% ultimately died from massive hemoptysis.

BAE may be technically challenging in certain situations. There may be several candidate vessels for the source of bleeding making the choice for BAE difficult. Also anomalous feeder vessels may be the source of bleeding and not found on angiography. Occasionally, the pulmonary artery is the bleeding source. The complication rate for BAE is small with notable examples. Inadvertent spinal artery embolization may occur resulting in paralysis. Focal headaches, reversible transverse myelitis, diaphragmatic paralysis and complications related to vascular access have been reported.

Although surgical intervention has decreased in the treatment of massive hemoptysis it is still a necessary component in the multidisciplinary therapeutic approach. In patients who are technically and physiologically operable and are not candidates for BAE or those who have failed BAE with multiple relapses, surgical intervention

should be strongly considered. Surgery is the treatment of choice in certain disease specific processes such as mitral stenosis and other cardiac etiologies. An important caveat in deciding between medical and surgical intervention is the aggressive nature of the hemoptysis and its physiological sequelae. If the bleeding is imminently life threatening or associated with severe physiological impairment, early surgical intervention should be strongly considered.

In summary, the diagnostic and therapeutic strategy for the successful treatment of hemoptysis is a multidisciplinary effort. The advancement of angiographic and endoscopic modalities has added to our therapeutic armamentarium. Local treatment strategies will depend on the availability of interventional radiologists, therapeutic endoscopists, surgical specialists and facility support.

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CHAPTER 24

Management of tracheobronchomalacia

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History

The history of tracheomalacia (TM) dates from 1897, when Czyhlarz first described the post-mortem finding of an unusually large trachea and bilateral bronchi. The first clinical report of isolated tracheal enlargement in an adult was by Mounier–Kuhn in 1932. Lemoine was the first to use bronchoscopy to describe acquired tracheal enlargement in the adult in 1949. Additional case reports of TM in adults began to appear in the 1950s. Ferraris described two patients with acquired TM who both reported "expiratory dyspnea," inability to clear secretions and recurrent respiratory infections. Both had been labeled and treated as asthmatics. Herzog described five patients with acquired TM, all of whom had stridor, cough and expiratory obstruction. On endoscopic evaluation, all of the patients had tracheal obstruction caused by the ballooning of the posterior membranous wall into the tracheal lumen during expiration.

Classification

Several classification schemes for adult TM have been proposed. Classification by macroscopic appearance is often employed, with lateral wall narrowing being called the "saber-sheath type" or "fissure shape" and the anterior–posterior wall narrowing being referred to as the "crescent type" or "scabbard shape." Some clinicians have included a third macroscopic designation for "circumferential" narrowing or labeled this appearance as a combination of the crescent and saber-sheath types. We prefer, as many of our predecessors have, classification into congenital forms (as in the Mounier–Kuhn disease) and acquired forms, such as those resulting from tracheostomy, chest trauma, chronic irritation, inflammation, mechanical anatomical factors or malignancy (Table 24.1).

Congenital or primary forms

Many of the congenital diseases and syndromes in which TM is seen in the pediatric population do not allow survival into adulthood. However,

Table 24.1 Classification of adult tracheomalacia.

Primary or congenital
Genetic, such as polychondritis
Idiopathic "giant trachea" or Mounier–Kuhn
Secondary or acquired
Posttraumatic
Post-intubation
Post-tracheostomy
External chest trauma
Post-lung transplantation
Emphysema
Chronic infection/bronchitis
Chronic inflammation
Relapsing polychondritis
Chronic external compression of the trachea
Malignancy
Benign tumors
Cysts
Abscesses
Aortic aneurysm
Vascular rings, previously undiagnosed in childhood

there are a small number that do and these are occasionally seen in clinical practice. These diseases include polychondritis, chondromalacia, Ehlers–Danlos and other congenital abnormalities of the cartilage, which weaken and result in dilation of the trachea. The resulting TM is often a lifelong issue for these patients.

There is one additional congenital condition that is not seen in children, but is found in the adult population. Idiopathic giant trachea, also known as Mounier–Kuhn syndrome or tracheomegaly, is a rare condition characterized by atrophy of longitudinal elastic fibers and thinning of the muscularis mucosa. This combination allows the trachea and central bronchi to dilate; however, there is a transition to the normal diameters in the peripheral airways. Up to 75% of patients with Mounier–Kuhn syndrome are diagnosed after age 28, with the majority diagnosed in the third or fourth decade of life. Patients with the syndrome have difficulty mobilizing secretions, recurrent infections, bronchiectasis and even pulmonary fibrosis. Tracheal diverticuli form secondary to the increased global compliance of the tracheal wall and the development of redundant membranous tissue.

To date, well over 100 cases of Mounier–Kuhn syndrome have been described in the literature. The disease is more frequently recognized with increased awareness of the disease and with the advent and more frequent use of computed tomography (CT) technology. The condition is not always apparent on plain chest radiographs. By CT, the diagnosis can be made when the right mainstem, left mainstem and trachea exceed 2.4, 2.3 and 3.0 cm, respectively, as these measurements represent three standard deviations above the upper limit of normal in adults. The cause is not known; however the first familial occurrence of the disease was documented in five patients with tracheobronchomegaly in 1965. Whether this occurrence constitutes a primary pathology or a predisposition to injury and subsequent development of a giant trachea is unknown.

Acquired or secondary forms

A variety of processes can cause secondary TM and tracheobronchomalacia (TBM) in adults (Table 24.1). Tracheostomy and endotracheal intubation can lead to frank weakening of the tracheal wall as a result of destruction and loss of the supporting cartilage. This malacia is most commonly 3 cm or less in length and is segmental in nature. Although some injuries heal, factors such as recurrent intubation, duration of mechanical ventilation and the use of high-dose steroids may predispose patients to developing progressive TM. The area of weakness can be seen at the stoma site and also at the inflatable cuff site. Occasionally, an additional abnormality may appear at the point where the tip of the tracheostomy tube impinges on the tissue. Possible causes of tracheal weakness in these areas include pressure necrosis, impairment of blood supply, recurrent infections and mechanical friction with resultant inflammation of the mucosa. Other forms of posttraumatic TM may result from any injury causing a loss of cartilage from the trachea, including external trauma and surgery, such as lung transplantation.

It is also suggested that chronic inflammation and irritants, such as cigarette smoke, are important contributors to the development of TM. A substantial proportion of patients with severe emphysema have some degree of malacia. The weakening of the tracheal wall may be related to the recurrent injury from cigarette smoke that leads to the emphysema, or it may merely be an extension of the peripheral hypermobility of the airways. Patients with chronic bronchitis may also have TM, thought to be secondary to the insult of recurrent infections, with or without cigarette smoking.

Additional etiologies for secondary TM exist. Chronic compression of the trachea resulting in TM most commonly results from benign mediastinal goiter, but it can also result from other sources of compression, including malignancies, abscesses and cysts. The literature also contains several reports of relapsing polychondritis, a disease characterized by recurrent inflammation and destruction of the cartilaginous structures (tracheobronchial chondritis). In fact, respiratory tract involvement in relapsing polychondritis occurs in up to 56% of cases, but the respiratory symptoms are found on presentation in only 14%. Patients with respiratory complications have a worse prognosis and poorer response to corticosteroids. To date, there have been 26 cases of vascular rings diagnosed in the adult population reported in the literature. These include double aortic arch and right aortic arch with an aberrant left subclavian

artery and ligamentum arteriosum. Compression by the vascular structure affects the integrity of the tracheal wall and increases the compliance over that in the adjacent tracheal tissue. As in children with vascular malformations, the resultant TM can cause respiratory symptoms, including dyspnea, recurrent pneumonia and stridor.

Incidence and natural history

Tracheomalacia and TBM in the adult population is not an uncommon disorder. The overwhelming majority of adults with TM and TBM have the acquired or secondary forms of the diseases. The true incidence of TM and TBM in adults is unclear because reports have been based on selected populations, rather than the population at large. In the late 1970s, Nuutinen and Jokinen greatly expanded the literature on acquired adult TM. Their data indicated that acquired TM was a disease of the middle-aged and elderly, most commonly seen in men over 40 years of age. Jokinen *et al.* reported finding TM in 50 of 214 patients (23%) with a history of chronic bronchitis who were examined bronchoscopically. Herzog reported TBM in 16 of 1500 patients (1%) undergoing bronchoscopy for various respiratory symptoms. In 1977, Jokinen *et al.* also reported bronchoscopic findings for 2150 Finnish patients with a range of symptoms and found that 94 (4.5%) had some form of malacia. Of these, TM was diagnosed in 21 (22%), TBM in 59 (62%) and isolated bronchomalacia in 14 (15%). TM was seen much more commonly in men (82%) as compared to women (18%), possibly reflecting the increased smoking prevalence in men at the time the study was conducted. The most recent incidence data is from Japan where collapse of the airway was greater than 50% in 542 of 4283 (12.7%) patients suffering from pulmonary disease who underwent bronchoscopy. In that study, 72% of patients were aged 50–80 years.

Tracheomalacia is progressive in some patients. Jokinen *et al.* performed repeat bronchoscopies on 17 of their patients with TM and TBM and found that severity had progressed in 13. Nuutinen reported a longitudinal study of 94 patients with TM and TBM with an average follow-up of 5.2 years. Of those who underwent repeat bronchoscopy, TM had progressed into TBM in 6 of 9 patients and bronchomalacia had progressed to TBM in all 5 cases. In no patient did the malacia improve. Some patients remained stable; however, the majority with mild to moderate disease worsened.

Symptoms

The main symptoms of TM in adults are cough, dyspnea, sputum retention, recurrent infection and hemoptysis. These symptoms are nonspecific and are often attributed to emphysema, chronic bronchitis, cigarette smoking or asthma. In fact, the patients may have coexistent emphysema, chronic bronchitis, or less commonly, asthma or bronchogenic carcinoma. These patients may exhibit evidence of collapse of the upper airway during forced exhalation. There may be inspiratory wheezing or stridor. An associated barking cough, which has been likened to a barking seal, has also been reported. In addition to the more nonspecific symptoms, episodic choking, chronic cough, recurrent pulmonary infections, syncope associated with forced exhalation or cough and even progressive hypercapnic respiratory failure have been reported. The disease can be unmasked by sedation and/or anesthesia or more commonly when the patient is stressed by infection such as bronchitis or pneumonia. In intubated patients, TM may not be evident because positive-pressure ventilatory support keeps the airway open. Once the positive pressure is removed, the patient may experience respiratory distress, wheezing and apparent stridor. Patients may be reintubated for these symptoms, and unexplained extubation failure should prompt evaluation for TM.

Diagnosis

Because airway deformation is a dynamic process that is accentuated by forced expiration, static chest radiographs often show no abnormality in primary TM or in TM due to other etiologies. Through the decades, a variety of radiographic techniques in addition to plain radiographs were used to diagnose TM. These included tracheograms, cinetracheograms and fluoroscopic studies. Today however, bronchoscopic visualization of dynamic tracheal or bronchial collapse remains the gold standard for diagnosing TM. Although some studies use

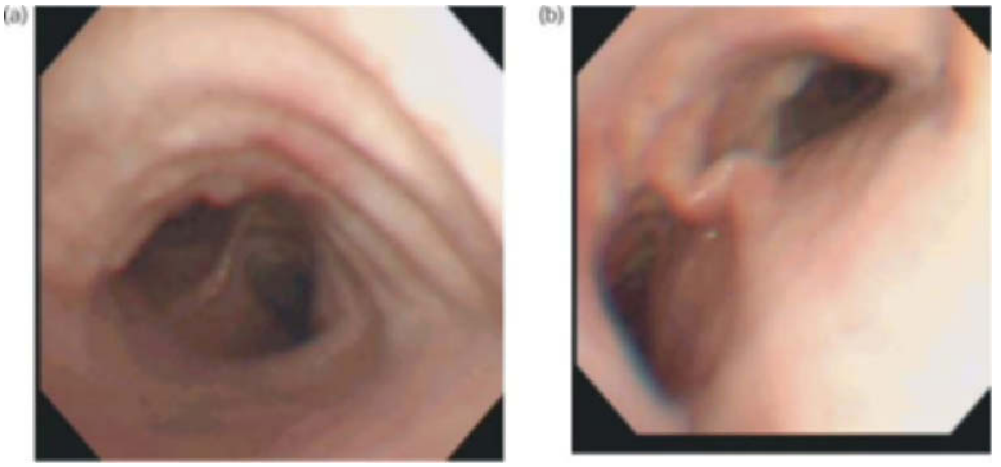

Figure 24.1 Bronchoscopic view of tracheomalacia. (a) Shows the normal status during inhalation; (b) shows near total collapse during quiet exhalation.

coughing, staining or other maneuvers to elicit airway wall collapse, the expiratory effort to achieve collapse has never been standardized. On direct visualization, the membranous trachea is widened and may be redundant (Figure 24.1a,b). There is obvious collapse of the airway during forced exhalation, and in some cases the airway lumen is completely obliterated as the membranous trachea collapses to the cartilaginous rings.

Emerging data suggests that dynamic CT images, although not the reference standard, are useful in diagnosing TM. There is published data on the normal trachea during forced exhalation defining the normal range of intrathoracic tracheal diameters and cross-sectional areas during forced maneuvers. Tracheal narrowing has been shown to be about 80% in a patient with TM versus 35% in 10 normal men. Based on this, some researchers have recommended using a cutoff of 70% or more narrowing on forced expiration as a diagnostic threshold for TM. The majority of investigators, however, have employed the criteria of more than 50% narrowing as a criteria for TM. Future studies of dynamic tracheal measurements involving a larger number of subjects of varying ages and both genders are necessary to more fully elucidate the normal range of tracheal collapsibility in the general population.

The recent development of multidetector CT scanners, which permit imaging of the entire central airways in only a few seconds, allows for volumetric imaging of the airways during a single dynamic forced exhalation maneuver. Using this method, researchers have reported agreement between dynamic expiratory CT findings and collapsibility seen during bronchoscopy. It has also been shown that low-dose CT technique is comparable to a standard-dose technique for measuring the tracheal lumen during the dynamic expiratory phase of respiration.

Dynamic magnetic resonance imaging (MRI) during forced expiration and cough to compare the collapsibility of the trachea in patients with TM to that of normal subjects has been studied. It has been shown that a coughing maneuver elicited a significantly greater degree of collapse than forced end-expiration. Because of its lack of ionizing radiation, MR has the potential advantage of allowing repeated assessments of the trachea during multiple respiratory maneuvers. Future studies comparing CT and MRI are necessary to determine the relative sensitivities and specificities of these methods for diagnosing TM with conventional bronchoscopy as the gold standard.

Although still in their infancy, multiplanar and three-dimensional CT reconstructions, including virtual bronchoscopy, are promising imaging methods for the evaluation of TM. Although axial images suffice for assessing the airways that are perpendicular to the axial plane (such as the trachea and bronchus intermedius), they are less

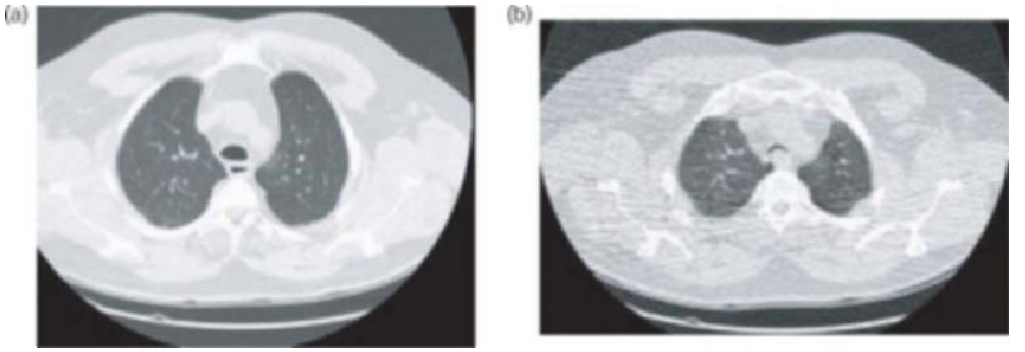

Figure 24.2 Two-dimensional CT airway reconstruction of the trachea. (a) Depicts the trachea in inhalation; (b) demonstrates tracheal collapse in exhalation.

than ideal for evaluating airways that course obliquely (such as the mainstem bronchi). Paired end-inspiratory and dynamic expiratory virtual bronchoscopy images provide an important complement to axial CT images for these portions of the airway (Figure 24.2a,b).

Pulmonary function studies may be useful in evaluating a patient with suspected TM, but they are not diagnostic. Spirometry most commonly reveals obstruction in proportion to the severity of malacia. The pattern is usually that of a decreased forced expiratory volume in 1 s and low peak flow rate with a rapid decrease in flow. Researchers have shown by esophageal balloon pressure measurements that the intrathoracic pressure is still rising sharply while the expiratory velocity begins to fall rapidly from its peak. This condition is an exaggeration of the normal pressure–flow relationship observed during the development of flow limitation. Decreased peak flow is thus characteristic of obstruction and hypercollapsibility of the airways. Lastly, flow oscillations, defined as a sequence of alternating decelerations and accelerations of flow, are often seen on the expiratory curve. These oscillations are not diagnostic of TM as they also can be caused by redundant pharyngeal tissue, as in obstructive sleep apnea syndrome, structural or functional disorders of the larynx and neuromuscular disease.

Treatment

The majority of adults with TM and TBM do not need therapy. The finding is often an incidental one. In a patient with symptomatic TM, care is initially supportive, unless the situation is emergent or rapidly progressive. As TM frequently occurs in patients who also suffer from chronic obstructive pulmonary disease, the obstructive disorder should be treated optimally first. Bronchospasm must be controlled as it results in large pressure swings in the thorax, thereby worsening the degree of collapse of the malacic tracheal segments. This increased airway resistance and work of breathing can lead to respiratory failure. Once chronic obstructive pulmonary disease has been controlled, a functional pulmonary baseline should be documented so that any response to an intervention for TM or TBM can be objectively evaluated.

If conservative measures fail, or if the patient is in critical condition, noninvasive positive-pressure ventilation (NIPPV) can be used short-term to keep the airway open and facilitate secretion drainage. Once bronchospasm and infection are under control, the patient can be transitioned to intermittent use of NIPPV until it is no longer needed. Intubated patients with known TM often benefit NIPPV upon extubation in an effort to prevent airway collapse, respiratory distress, wheezing and increased work of breathing which can lead to extubation failure.

In selected patients, surgery may be employed. Tracheostomy alone may be effective because the tracheostomy tube might either bypass the malacic segment or the tube itself might split the airway open. If the patient has generalized and extensive TM, a longer tube may be necessary as most of the more commonly used tubes are too short to prevent distal collapse, despite providing adequate proximal stenting. A tracheostomy also provides

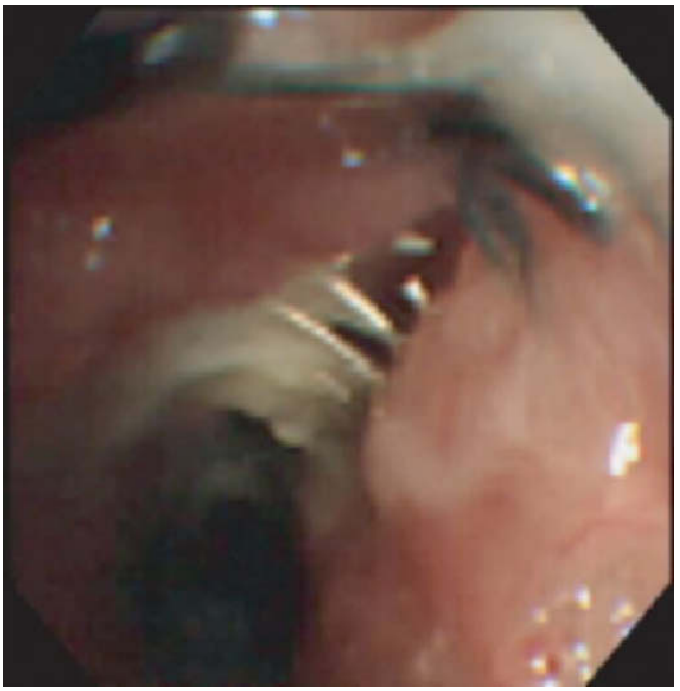

Figure 24.3 Image of a patient with long-term stent complication. Visible are stent fractures with surrounding granulation tissue and purulent secretions. The airway prosthesis had to be removed.

easy access for positive-pressure ventilation if required to maintain an open airway. Unfortunately, tracheostomy may actually aggravate the underlying disorder, and is therefore not a first-line treatment.

Although bone grafts were initially used, surgical support of the pars membranacea has been performed with a variety of prosthetic and autologous materials. Amedee *et al.* described 16 patients with TM who were treated with tracheal implantation of biocompatible ceramic rings. The procedure was successful in all patients, and reintubation or tracheostomy was not necessary in the 6.4 years of follow-up. Additionally, 3 patients who had been tracheostomy dependent prior to the procedure tolerated decannulation after the surgery.

Recently, surgical placation of the posterior wall of the trachea with Marlex mesh has received attention. In that procedure, access is through a right posterolateral thoracotomy and the mesh is fashioned into a 2.5-cm wide strip which is sutured to the posterior membranous wall. Thereafter, 2.0-cm sheets of mesh can then be sutured to the right and left mainstem bronchi. At our institution, this procedure is offered to patients who are good surgical candidates and in whom central airway stenting has improved symptoms. Conventional resection and reconstruction can be considered for focal malacia of the trachea.

An array of stents can be used to keep the airway open mechanically. Metal stents have been used to manage airway obstruction from many causes. They are easily placed by flexible bronchoscopy, are visible on plain radiographs and expand dynamically. The most common complications with metal stents is the formation of granulation tissue, which may or may not require intervention, and breakage over time, which can cause severe problems including airway obstruction and airway perforation (Figure 24.3). These disadvantages, coupled with the fact that metal stents can usually not be removed easily, do not make them an attractive first choice for patients with TM. Silicone stents, on the other hand, are easily inserted, repositioned and removed. These stents are best placed using rigid bronchoscopy and general anesthesia. Although silicone studs on the surface of the stent retard migration, stent migration is still

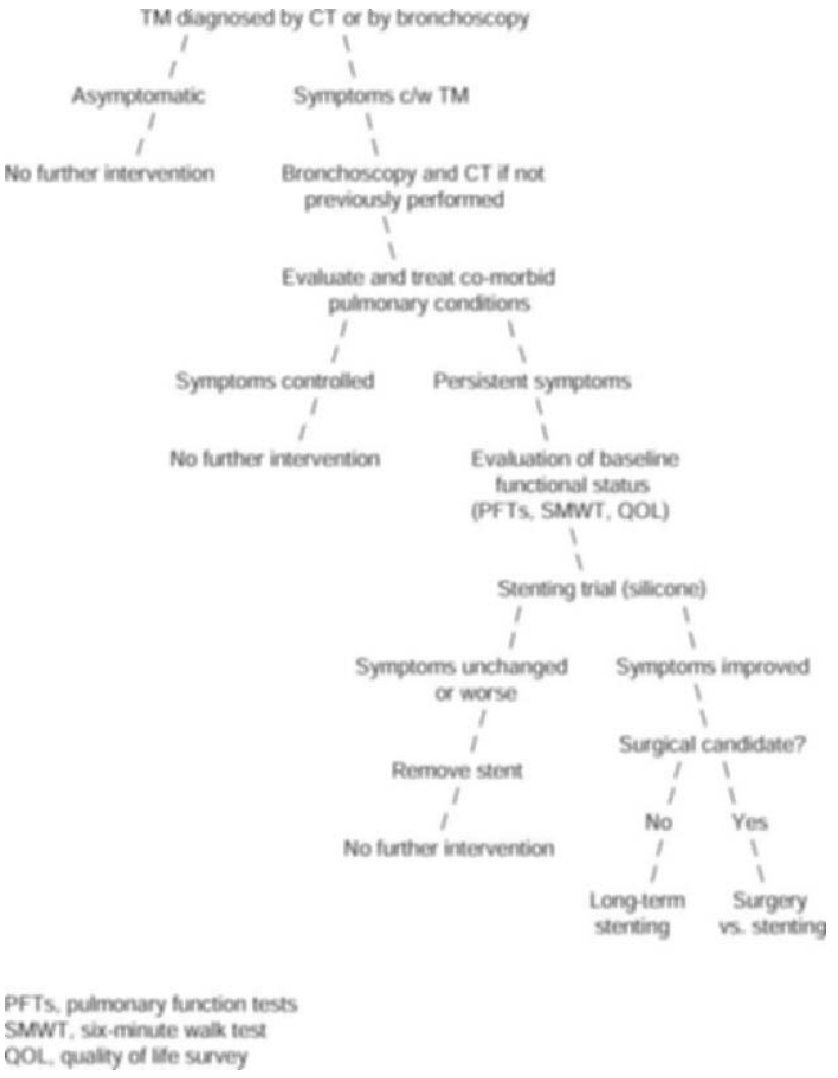

Figure 24.4 Treatment algorithm for adult tracheomalacia.

common and may be heralded by a new cough. This problem requires direct visualization and either repositioning, removal or replacement of the stent. Hybrid stents and biodegradable stents are now being developed, but their utility for this disorder has not yet been evaluated.

Published studies have employed both subjective and objective means to evaluate the efficacy of stent placement for benign airway stenoses. TM has been included in many of these studies, however there are no large series on TM alone. To describe the benefits of stent placement, clinicians have used improvement of respiratory symptoms, clearing of infectious processes and lack of stent complications as endpoints.

Most patients report immediate improvement in their respiratory symptoms once the stent is placed. Stents can immediately improve airflow dynamics in patients with benign airway obstruction, including TM, but success is not universal. Gotway *et al.* reported long-term pulmonary function data with stents placed for both stenotic and malacic

lesions. At a mean of 15 months after stent placement, FEV_1, $FEF_{25–75}$ and peak flow parameters had declined, despite the patients' ongoing subjective improvement. O'Donnell *et al.* measured tracheal transmural pressure with esophageal balloons, assessed the cross-sectional shape of the trachea and measured the critical pressure required to produce maximum expiratory flow in TM patients before and after stenting. It was hypothesized that critical pressure for flow limitation occurs before central airway collapse. In such circumstances, stenting the airway is unlikely to improve maximal expiratory flow. Therefore, a low critical pressure may be a marker for therapeutic failure.

If airway stenting does not improve symptoms or the functional baseline of the patient, the stents should be removed to avoid any stent-related complications. At our institution, airway stenting is mainly used to identify the individual most likely to benefit from airway stabilization. If improvement is present and the patient is a good surgical candidate, surgical tracheoplasty is the preferred goal. If the patient improves but declines surgery, long-term stenting can be utilized, most commonly with silicone stents. Very rarely will metal stents have a role in the long-term management of this benign disorder. An algorithm of our approach to the patient with TM is outlined in Figure 24.4.

Conclusion

Tracheomalacia and TBM are becoming more commonly recognized and treated in adults. The causes and therefore treatments vary, so a working knowledge of the options is important. Noninvasive imaging technology is increasingly employed for diagnosis, and novel treatments, such as definitive surgical placation and stabilization with removable stents, are becoming alternatives to conservative interventions, such as continuous positive airway pressure (CPAP). As a result of the complexity of the condition and its treatment options, these patients may best be assessed and managed individually in centers specializing in complex airway disorders.

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