Thoracic Endoscopy: Advances in Interventional Pulmonology
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
Thoracic Endoscopy: Advances in Interventional Pulmonology

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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 bronchoscopy. In the first chapter, a method for detecting occult malignancies (auto-fluorescence 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
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.

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PART I
Advances in diagnostic bronchology
CHAPTER 1

Autofluorescence in the detection of lung cancer

Michael J. Simoff, MD

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].

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Moderate dysplasia (%)</th>
<th>Severe dysplasia (%)</th>
<th>CIS ≥2 foci (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100</td>
<td>14</td>
<td>11</td>
<td>15, 15</td>
</tr>
<tr>
<td>II</td>
<td>46</td>
<td>18</td>
<td>4</td>
<td>13, 24</td>
</tr>
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<td>III</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>10, 20</td>
</tr>
<tr>
<td>IV</td>
<td>67</td>
<td>36</td>
<td>15</td>
<td>5, 13</td>
</tr>
</tbody>
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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.

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 carcinization 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].

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 mm² in surface area. Endobronchial changes less than 10 mm² 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.

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
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 predominant 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 predominant 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 metalloproteinase 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].
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
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
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 (Pentax 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
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...
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, Tuttingen, 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