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Fluorescent bronchoscopy

Sebastien Gilbert, MD, James D. Luketich, MD, Neil A. Christie, MD*

Division of Thoracic and Foregut Surgery, University of Pittsburgh Medical Center, 200 Lothrop Street, Suite C800, Pittsburgh, PA 15213, USA

Long-term lung cancer survival in North America remains less than 15% and has not changed appreciably over the past several decades [1]. It is anticipated that the number of patients who have lung cancer will continue to rise in North America over the next 15 years despite the gradual decrease in the proportion of people who smoke because the risk of lung cancer remains elevated in previous smokers. If current smoking trends continue to show a decline, the majority of cancers seen in the future will be in previous smokers [2]. Given the ineffectiveness of treatment for advanced cancer, early lung cancer detection and treatment offer the greatest potential for achieving a decrease in lung cancer mortality.

Detection of lung cancer at an earlier stage should result in improved survival and the opportunity for less invasive therapy such as thoracoscopic resection of peripheral tumors and endobronchial ablative therapy for central airway tumors. Experience with screening and early diagnosis and treatment in other epithelial organs such as the cervix have shown that early detection and treatment of lesions can be accomplished with improved cure rates [3]. Based on calculations of estimated tumor doubling times, it is estimated that a tumor will grow for months or even years before reaching a size detectable with standard imaging techniques [4], which should allow a significant window of time in which to detect early tumors in high-risk patients. Large lung cancer screening trials evaluating sputum cytology and chest radiography resulted in earlier diagnosis with improved survival in identified patients, but no difference in overall survival when compared with control patients [5–7]. Based on these results, there are currently no recommendations for lung cancer screening. There has been a resurgence of interest in screening for lung cancer, however, with the advent of more sensitive screening tests such as CT and fluorescent bronchoscopy. While CT scans can identify subcentimeter parenchymal nodules accurately, early endobronchial lesions and central tumors are not seen well [8]. Sputum cytologic analysis offers the detection of clinically occult lesions, but it cannot localize the lesion in the airway. In situ and microinvasive cancers might not produce visible abnormalities on standard white-light bronchoscopy (WLB). Even with multiple bronchoscopies or selective segmental bronchial brushing, the source of cytologically abnormal cells can be difficult to localize. Fluorescent bronchoscopy offers the potential for more accurate discovery and localization of early tumors and premalignant epithelial changes which are generally not well seen with WLB. In a study by Woolmer [9], only 29% of carcinoma in situ (CIS) detected by sputum cytology examination could be localized by conventional WLB.

Fluorescent bronchoscopy

Fluorescent bronchoscopy uses the observation that dysplastic tissue and areas of CIS demonstrate weaker green fluorescence than normal tissues when illuminated with blue light. Fluorescent properties of human tissues have been the object of scientific interest since the early 1920s [10]. Early attempts at endobronchial surveillance used fluorescent dyes. Current fluorescent bronchoscopy exploits the autofluorescence characteristics of premalignant and malignant lesions of the bronchial mucosa, and no exogenous dyes are required. The best-known fluo-

* Corresponding author. Shadyside Medical Center, 5200 Center Avenue, Suite 715, Pittsburgh, PA 15232.
E-mail address: christiena@upmc.edu (N.A. Christie).

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rescent bronchoscope that works on this principle is the lung imaging fluorescence endoscope (LIFE, Xillix Technologies Corp, Vancouver, British Columbia, Canada), which was developed by Dr. Stephen Lam at the British Columbia Cancer Agency [11]. The LIFE system uses tissue fluorescence to localize suspicious lesions in the tracheobronchial tree. A helium–cadmium laser light source projects light at a wavelength of 442 nm [12] to induce tissue fluorescence. Two cameras, one with a red filter and one with a green filter, capture the fluorescent signal. The ratio between the red and green fluorescence is used to distinguish benign from malignant tissue. Real-time digitized images are constructed using the relative intensities of red and green fluorescence, and a nonlinear analysis combines the red and green fluorescence intensity values to create a single number that discriminates between normal and abnormal tissue sites. A computer-enhanced pseudoimage is created, allowing the delineation of abnormal areas when displayed on the monitor. Suspicious areas appear reddish-brown and normal areas appear green. Abnormal-appearing mucosa can then be biopsied to identify dysplastic areas, CIS, or microinvasive cancers.

LIFE bronchoscopy represents the evolution and refinement of existing fluorescence imaging concepts and techniques rather than a novel diagnostic imaging modality. Normal tissue produces significantly higher fluorescence intensity than dysplastic lesions or CIS, particularly in the green region of the emission spectrum [11,12]. Decrease in the autofluorescence in early cancer or dysplastic tissue is likely a result of multiple factors. Most of the fluorescent signal originates from the submucosa. The loss of autofluorescence, as evidenced by a reddish-brown image on the LIFE endoscope, might be related to destruction of the extracellular matrix by metalloproteinases [13]. Increased bronchial microvascular density and impaired transmission of fluorescent signal through a thickened malignant or dysplastic epithelium might also contribute [14].

The SAFE 1000 (Pentax, Asahi Optical, Tokyo, Japan) and the D-light (Storz, Tuttlingen, Germany) are other commercially available systems.

Bronchoscopic technique

Bronchoscopy is performed on an outpatient basis using local anesthesia with or without intravenous sedation. It is combined with a conventional WLB examination and adds approximately 15 minutes to the overall procedure time [15]. An Olympus BF20 (Olympus America, Melville, New York) is used. During a LIFE examination, areas of normal green fluorescence are labeled class I (normal), whereas areas of increased redness with indistinct borders are labeled class II (abnormal). Class III lesions (suspicious) show deeper red coloration and distinct borders. This classification scheme was described by Lam in 1998 [15]. Most LIFE bronchoscopists would agree that there is a learning curve of approximately 20 examinations, during which accuracy improves consistently. The biopsy specimens obtained during LIFE bronchoscopy should be interpreted by lung pathologists according to defined criteria published in the World Health Organization lung tumor classification [16]. Preneoplastic lesions include squamous dysplasia and CIS. Four grades of preneoplastic lesions have been defined (ie, mild, moderate, severe dysplasia, and CIS) based on the distribution of atypical cells and mitotic figures. Although the reproducibility of this system remains to be established, it is part of a concerted effort to achieve a standardized framework for classification [16]. Inconsistency in pathologic classification can confound study results, and some studies have shown interobserver variability on the pathologic classification.

Prebronchoscopy risk stratification

The success of any screening program depends on the prescreening risk of cancer in the group being evaluated. Although 80% of lung cancers are attributed to smoking, less than 20% of smokers develop lung cancer in their lifetime. The yearly incidence of lung cancer in the general population of the United States is 0.05% to 0.09% [1]. Epidemiologic studies show that an increased risk of lung cancer is seen in patients who have more extensive smoking histories. Presence of chronic obstructive pulmonary disease has also been associated with an increased risk of lung cancer. Previously treated primary lung cancer also represents a risk factor for second primary lung cancer. Clinically significant second primary lung cancers are diagnosed in patients who have prior non–small-cell lung cancer at a rate of 1% to 3% per patient per year. Despite postoperative follow-up care, only 50% of second primaries are resectable. At the time of diagnosis 19% of these cancers are locally advanced, 65% are associated with metastatic disease, and 20% occur in patients who are not surgical candidates because of insufficient pulmonary reserve. The 5-year survival rate after complete resection of a second primary lung cancer is only 20% [17]. Sputum screening with conventional cytology can identify

patients who are at high risk for endobronchial neoplasia or dysplasia, and sputum immunostaining promises even greater sensitivity. Experiments with monoclonal antibody 703D4 have shown that overexpression of an RNA binding protein, hnRNP A2/B1, is a powerful predictor of early subclinical cancer in high-risk groups [18].

Chemoprevention

Saccomanno observed in longitudinal studies that abnormal bronchial epithelial cell changes predated development of invasive lung cancer [19,20]. It is now believed that lung cancers develop through a series of sequential morphologic changes from metaplasia to dysplasia to CIS before the development of invasive cancer. Bronchoscopic identification of these premalignant lesions can be used to identify patients for chemopreventative therapy or sequential monitoring. Longitudinal monitoring of these patients should identify early cancers when and if they appear and allow clinicians to observe the natural history of these lesions. Ten percent of patients who have moderate dysplasia and 40% to 83% of patients who have severe dysplasia progress to invasive cancer [21]. Based on autopsy studies of the tracheobronchial tree of smokers performed in the 1960s and 1970s, the incidence of CIS is probably between 2.2% and 22.5% [22]. The exact proportion of patients who have CIS in whom disease will progress to invasive cancer is not known. There have been reports that some individuals continue to show malignant cells in sputum for several years without symptoms or abnormality on chest radiograph. Frost showed that only 43% of smokers who had marked dysplasia on sputum cytology developed cancer over a 10-year follow-up period. Saccomanno noted progression from dysplasia to cancer in only three of 16 uranium workers [23]. This variability underlines the lack of knowledge of the natural history of premalignant changes in the tracheobronchial tree. The variability in incidence might reflect a lack of standardization in the pathological definition of CIS over the years. It is possible that a significant proportion of these lesions were initially misclassified and that the prevalence of CIS in the tracheobronchial tree of smokers has been overestimated. This theory is corroborated by the observed incidence of lung cancer, which is much lower than the reported rate of CIS. The incidence of second primary lung cancers should also be higher than the reported 1% to 4% per year [17,24,25]. A more recent observational study of bronchial CIS suggested that such lesions almost uniformly progress to microinvasive carcinoma. LIFE should allow localization, and longitudinal follow-up of these lesions which will allow clinicians to learn about the natural history of these lesions and their risks of progressing to invasive cancer.

Improved identification of dysplastic premalignant lesions will provide an opportunity to intervene with chemoprevention therapy to try to halt the progression from dysplasia or CIS to invasive cancer [26]. Chemoprevention, treatment directed at stopping the progression of multistep lung carcinogenesis, will require a better understanding of the biology of premalignant bronchial lesions and the development of effective chemopreventative agents. Identification of patients who have early endobronchial lesions can be used to validate less invasive assays on sputum or blood, which can be evaluated in parallel to the pathologic and cytologic changes occurring in bronchial epithelium and epithelial cells.

Clinical trials with lung imaging fluorescence endoscope bronchoscopy

A large experience with LIFE bronchoscopy has been reported in the literature. Generally, it attests to the improved sensitivity of LIFE bronchoscopy over standard WLB in detecting dysplasia and CIS. One study involving 173 high-risk patients from seven centers in the United States and Canada demonstrated that the combination of WLB and LIFE bronchoscopy improved clinicians' ability to detect premalignant and early-stage malignant bronchial lesions endoscopically [15]. In that group of patients, WLB had a sensitivity of 9% for detecting moderate/severe dysplasia or CIS and a sensitivity of 65% for detecting intraepithelial neoplasms and microinvasive carcinoma. The addition of LIFE bronchoscopy to WLB yielded sensitivity values of 56% and 95% for preinvasive and invasive lesions, respectively, which represents a 6.3-fold increase in the detection of intraepithelial lesions and a 1.5-fold increase in the detection of preneoplastic lesions. These results confirm the difficulties in detecting early neoplastic lesions by conventional bronchoscopy alone. Thirty-nine percent of patients who have abnormal sputum cytology will require more than one WLB to identify an associated neoplastic lesion, even if more than half of these lesions have progressed beyond the CIS stage [27]. LIFE bronchoscopy can help overcome this lack of sensitivity and allow histologic follow-up of premalignant lesions that would otherwise be undetectable with WLB. This information will be helpful in characterizing the natural history of these lesions.

LIFE bronchoscopy has also been compared with WLB in a randomized fashion [28]. The aim of the trial was to assess the efficiency of each technique in detecting premalignant lesions of the airways. It included 55 patients who were considered to be at high risk for lung cancer because of smoking history (age >30; 7.1 pack-years mean smoking history), documented airflow obstruction, and abnormal sputum cytology (87%) or a past history of lung cancer. Each patient was randomized to LIFE or WLB, and each examination was performed by a different bronchoscopist. The operator was blinded to the results of the previous examination. A mean of seven biopsy specimens was retrieved per patient. The sensitivities of LIFE alone (68.8%) and that of LIFE combined with WLB (81.3%) were significantly higher than that of WLB alone (21.9%), but the combined examination was significantly less specific than WLB alone (47.8% versus 78.3%). In this trial, neither the order in which the procedures were performed nor the bronchoscopist had a significant impact on sensitivity and specificity.

Other published studies corroborate the enhanced ability of LIFE to detect premalignant lesions [29,30]. On average, LIFE examination leads to more biopsies because more areas of mucosa appear abnormal. An argument can be made that the improved sensitivity is merely related to the fact that more areas of the airway are biopsied during LIFE. When specificity is taken into account, however, and detection ratios of LIFE and WLB are compared, the difference in effectiveness remains significant [29]. Similar results have been published by other groups [25,26,31–33]. The sensitivity of LIFE ranged from 73% to 89%, and the specificity ranged from 46% to 61%. Once again, the addition of LIFE to WLB improved the sensitivity of the bronchoscopic examination [29–31,33]. One study failed to demonstrate increased sensitivity with LIFE bronchoscopy [34]; however, this might be explained by the selection of a relatively low-risk population compared with other trials (ie, >20 pack-years smoking history alone).

The performance of LIFE bronchoscopy is related directly to the operator's skill and experience with the technique. Scope-induced trauma or other artifacts can easily be mistaken for an area of abnormal fluorescence. Although biopsy of these areas will undoubtedly help maintain a high sensitivity, it will potentially increase the number of false-negatives (ie, decrease sensitivity). In the authors' experience, the incidence of fluorescent anomalies might be higher when LIFE is performed after WLB, which is most likely related to scope-induced mucosal trauma. Lastly, the problem of low specificity is not unique to LIFE as a screening test. CT scanning for early lung cancer, mammography for breast cancer, and prostate specific antigen (PSA) for prostate cancer are noteworthy examples of relatively nonspecific screening tests [8,31]. The result of decreased sensitivity is the taking of additional biopsies that do not pose a significant risk to the patient. The development of quantitative fluorescence and the use of nebulized photosensitizers and endobronchial ultrasonography might help overcome some of the specificity limitations.

Lung imaging fluorescence endoscope bronchoscopy for cancer staging

A recent study found that LIFE bronchoscopy was useful in staging early endobronchial lesions and determining which lesions were amenable to endobronchial therapy as opposed to more invasive therapy [35]. Twenty-three patients who had radiologically occult tumors who were referred for endobronchial therapy were evaluated with LIFE bronchoscopy. On high-resolution CT scanning, radiologically apparent disease (lymph nodes or primary tumor) was detected in four patients. The remaining 19 patients were evaluated with fluorescent bronchoscopy. Six patients had tumors less than 1 cm in diameter, and the distal margin of the lesion could be seen bronchoscopically. These patients were treated with endobronchial therapy. The remaining patients had more extensive disease on LIFE bronchoscopy. Six of the 13 patients underwent surgical resection of T1 or T2 node-negative tumors. On patient had stage II N1 disease. The remaining patients were medically inoperable and were treated with external beam radiation (n = 4) or endoluminal therapy (n = 3). Of the localized tumors treated with endoluminal therapy, no recurrence was seen within a 30- to 50-month follow-up period.

High-resolution CT and fluorescent bronchoscopy offer the ability to better stage patients who have radiologically occult lung cancer, preventing and identifying the subset of patients who can be treated endobronchially with a good expectation of cure.

Another circumstance in which LIFE bronchoscopy has been evaluated is in the preoperative assessment of patients who had known lung carcinoma to detect synchronous primary tumors [36]. Seventy-two patients who had known lung cancer (69 non–small-cell; three limited-stage small-cell) were evaluated with LIFE bronchoscopy and WLB. Three synchronous cancers were detected, one by WLB and LIFE and two by LIFE bronchoscopy alone. Two of the three patients had squamous cell

primary cancer. The third tumor was not subclassified histologically. Two of the three patients had advanced cancers. One patient died of postobstructive pneumonia before the initiation of any therapy and another patient had advanced nodal disease that precluded resection. A third patient underwent right pneumonectomy followed by endobronchial therapy for a small lesion identified with LIFE bronchoscopy. The authors recommended LIFE bronchoscopy to evaluate for synchronous occult lung cancers, but only immediately before surgery after all other staging procedures had been completed.

University of Pittsburgh experience

At the University of Pittsburgh, LIFE bronchoscopy was used to screen patients for the occurrence of second primary lung cancer following pulmonary resection for non–small-cell lung cancer between 1997 and 2002. The initial experience has been reported [37]. Ninety-five patients participated in the screening program. Fifty-five had resected adenocarcinomas and 40 had resected squamous cell carcinomas. The examination frequency was annually if no abnormalities were identified. Seventy-four percent of patients had stage I cancer, 18% had stage II cancer, and 8% had stage III cancer as their initial primary cancer. Seventy-two percent of patients had undergone previous lobectomy, 6% had undergone pneumonectomy, and 22% had undergone segmental resection. Of the 12 abnormal areas identified pathologically (high-grade dysplasia, CIS, or microinvasive cancer), six were detected with the fluorescent examination and four with WLB with sensitivities of 50% and 33%, respectively. Fig. 1 shows an endoscopic view of an area of CIS that was occult on WLB. Fig. 2 shows the identical area on LIFE bronchoscopy, in which the abnormality was visualized. The specificity of fluorescent bronchoscopy was 76% compared with 98% for WLB. Nine of 95 patients (9%) had lesions for which treatment could be considered. The poor sensitivity of WLB in this group of patients might, in part, have been related to the fact that two or three random biopsies were taken in every patient, increasing the potential of identifying bronchoscopically occult lesions.

Fig. 1. Conventional WLB.

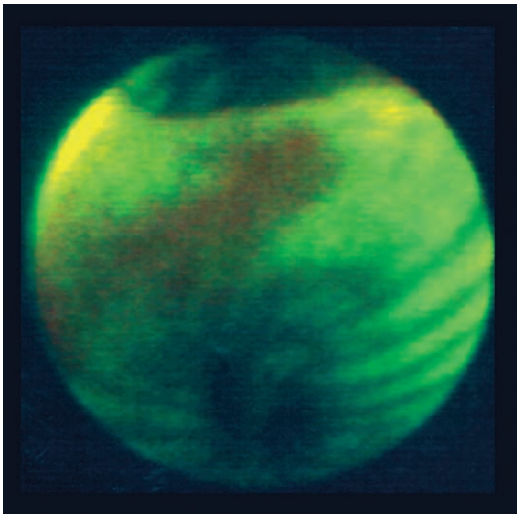

Fig. 2. LIFE bronchoscopy image corresponding to image in Fig. 1.

Future directions

The evolution of LIFE technology toward a more objective quantification of tissue fluorescence and the addition of other complementary endoscopic tools such as endobronchial ultrasound might improve the specificity of the technique, which would ultimately benefit patients by decreasing the number of biopsies performed and the time requirement for the examination. With an emphasis on screening and early diagnosis, clinicians might see more patients who have radiologically occult lesions who will be potential candidates for endobronchial therapy for attempted cure. One of the major challenges in achieving widespread integration of this modality in clinical

practice is delineation of the subgroups of patients who are at higher risk of developing lung cancer, who are appropriate patients for this invasive and relatively labor-intensive evaluation.

Endobronchial biopsy specimen evaluation with methods other than histologic evaluation potentially offers a fruitful opportunity. Molecular abnormalities have been observed in patients who have histologically normal epithelium and might represent a more suitable marker than histologic patterns, which do not always correlate predictably with outcome [38]. Cellular changes in gene copy number, gene expression, and protein profiles might represent better predictors of progression of dysplasia and CIS and act as surrogate markers for efficacy in chemoprevention studies [39]. That cytogenetic changes are occurring with associated molecular alterations is compatible with the current understanding of the molecular pathogenesis of cancer [40]. The ability to sample preneoplastic lesions accurately for molecular and histologic analysis and to follow their progression or regression longitudinally should prove to be valuable tools in outcomes research. Multiple chromosomal abnormalities have been noted and gene mutations have been detected using sensitive molecular techniques such as polymerase chain reaction [39]. The results of these molecular studies have so far failed to identify a single marker that is expressed consistently in cancers or dysplastic lesions but not seen in normal endobronchial cells, and no markers seen in dysplastic cells have been reliably predictive for progression to cancer. With the development of comparative genomic hybridization techniques, clinicians have the potential to get a much broader picture of total genomic damage patterns, which might be more predictive [41]. New techniques of comparative analysis of gene expression across thousands of genes [42] and new methods of proteomic analysis might also be adapted to these samples [43]. With this large amount of additional information, a predictive molecular signature of lesions that are likely to progress to cancer could be identified. The addition of these newer methods of tissue analysis should stand to improve the utility of LIFE bronchoscopy in the future in clinicians' attempts to decrease the mortality from lung cancer and facilitate less invasive endobronchial treatments.

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