Review of Recent Advances in Fluorescence Bronchoscopy in Early Localization of Central Airway Lung Cancer

TIMOTHY C. KENNEDY,a STEPHEN LAM,b FRED R. HIRSCHc

aDivision of Pulmonary and Critical Care, University of Colorado Health Science Center, Denver, Colorado, USA; bUniversity of British Columbia and the British Columbia Cancer Agency, Vancouver, British Columbia, Canada; cUniversity of Colorado Cancer Center, Denver, Colorado, USA

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ABSTRACT

Centrally located lung cancers are radiologically occult until so far advanced as to have a low cure rate or require extensive resection for cure, but at a cost of high morbidity. These cancers represent about one-fifth of new lung cancers.

Autofluorescence bronchoscopy appears to be an important tool in localizing premalignant and early malignant lesions in the large central airways, particularly when applied to high-risk patients. Applications include studies of molecular biology of premalignancy and early malignancy, chemoprevention studies, endobronchial therapy studies, localization of synchronous tumors, estimation of the extent of field cancerization, and better estimation of resection margins. Autofluorescence bronchoscopy appears to be significantly more sensitive than white light examination but has low specificity. This technology is likely to gain widespread use when evaluation of sputum for malignant changes is both more sensitive and specific, and when its application is demonstrated to reduce mortality in this important subgroup of non-small cell lung cancer patients. The Oncologist 2001;6:257-262

INTRODUCTION

Any review of the innovative new technology of autofluorescence bronchoscopy must occur within the context of its value in identifying and treating early hilar lung cancer (EHLC). Any review must also address the concept that lung cancer often occurs in the large central airways as well as the periphery, the latter of which is more commonly amenable to detection by helical computerized tomographic (CT) scanning.

REVIEW OF EFFORTS TO DETECT EARLY LUNG CANCER

Effective early detection of lung cancer is now being reconsidered as a possibility, and currently renewed interest in designing and funding population-based clinical trials has engendered international attention. The studies by Kaneko [1], and subsequently Henschke [2] are the main driving forces of this excitement, demonstrating that use of helical CT scanning in uncontrolled pilot studies remarkably increased sensitivity in finding early peripheral lung cancer. These discussions, as to the potential value of screening, have intensified in the context as follows:

• New technologies are now available which clearly have a higher degree of sensitivity to detect early disease;
• Advocacy groups raising the question about why studies are not being funded to address a disease causing more mortality than breast cancer, colon cancer, prostate cancer, and all the lymphomas and leukemias lumped together;
• Remarkable advances in the understanding of molecular events of malignancy;
• Improved endobronchial therapies for early large airway disease, and
• Improved techniques for surgical resection.
At this time neither the American Cancer Society nor the National Cancer Institute (NCI) in the U.S. recommend any attempt to identify lung cancer at a limited or resectable stage. This is because three large, randomized, controlled studies conducted by the NCI failed to show a mortality reduction benefit with interval chest radiographs and sputum cytology [3-5]. A subsequent study from Czechoslovakia provided similar conclusions [6]. These discouraging results occurred in spite of reduced case rate fatality and a marked shift toward earlier more resectable disease at the time of diagnosis.

There have been a number of valid criticisms of these studies including that the studies were underpowered considering current knowledge of high risk, the quality of the sputum cytology evaluations, control contamination, and low compliance in the screened group [7].

Recently an additional concern regarding overdiagnosis bias or length-time diagnosis bias accounting for the results of the Mayo study was addressed by a long-term follow-up review by Marcus et al. [8]. Their analysis suggested that overdiagnosis bias accounted for the failure of mortality benefit in spite of a higher number of resectable cases found in the screened group. In this analysis, length-time bias was not excluded as an alternative explanation. What is not resolved is whether imprecision as to the cause of death (lung cancer or from a fatal comorbid condition) contributed to these results. Since there was a statistically insignificant increase in lung cancer mortality in the screened group, the possibility of excess mortality resulting from treatment of relative benign subsets of lung cancer has been suggested.

Since early stage is well-established as the best predictor of favorable outcome in non-small cell lung cancer, and since more subjects had early stage disease and lower case fatality in the screened group, an argument can be made that there may be an adverse consequence of early diagnosis. The explanation for this remains elusive and controversial. Both overdiagnosis bias and length-time bias explanations rely on the premise that there is a large population of benign forms of lung cancer, detectable by chest x-ray and/or sputum cytology, that will never cause mortality in the diagnosed patient. This is not, however, the experience of the pulmonary, medical oncology, nor thoracic surgery clinical community, particularly with respect to lesions detected by chest radiograph.

It is possible that overdiagnosis bias is relevant to central airway carcinoma in situ (CIS) or small lung nodules detectable on low-dose spiral CT, but not likely for central airway stage 1 invasive carcinoma. The importance of overdiagnosis is likely much less for central airway CIS compared to peripheral tumors because these lesions can be easily treated with endobronchial therapy such as electrocautery or photodynamic therapy without loss of adjacent normal lung tissue [9-12].

Unlike thoracotomy and lung resection, these endoscopic therapies have much less potential for procedure-related death and cause minimal discomfort to the patients.

**White Light Bronchoscopy for Detection of EHLC**

Because the Japanese health care system continued mass screening for lung cancer using sputum and chest x-rays [13] in spite of the NCI findings, and because Bechtel and Saccomanno’s group [14] in Grand Junction, Colorado continued to evaluate high-risk populations with sputum cytology, additional outcome experience has been accumulated using sputum followed by white light bronchoscopy. These studies reinforced the findings of the NCI studies that those patients who were radiologically occult but sputum-positive for cancer had a very favorable outcome. Most of the lesions found in this way were squamous cell carcinomas. In the case of the Grand Junction group, many of the patients had significant exposure to inhaled uranium radiation in addition to tobacco.

These successful results were achieved with white light bronchoscopy by bronchoscopists skilled in finding very subtle changes in bronchial mucosa. They repeated examinations as needed until the lesion was localized. Often local therapies were effective. These favorable experiences with sputum cytology analysis followed by bronchoscopy have led to a proposed new stage category in lung cancer by Watanabe et al. [15] termed “EHLC.”

In spite of these favorable results, the NCI studies by Johns Hopkins Hospital (Baltimore, MD) and Memorial Sloan-Kettering Cancer Center (New York, NY) did not show that adding sputum cytology evaluations to screening improved mortality reduction over chest x-rays alone. Low sensitivity of sputum cytology was problematic in these studies. An additional concern was that a significant contributing factor to these poor results was the failure to localize these lesions early enough. These lesions presumably had time to become significantly more invasive. Woolner et al. showed that CIS was visible to experienced bronchoscopists only 29% of the time [16]. The paradox of favorable mortality outcomes using white light in spite of the Woolner group’s low yield may be best explained by overdiagnosis or length-time bias rather than late diagnosis. The very high survival rates in studies without randomized control groups are difficult to reconcile with the failures to reduce mortality in screening studies using sputum cytology that have randomized, controlled design. It is likely that the main reason for these results is that the relatively low smoking histories of subjects underpowered the studies’ capacity to evaluate the impact of sputum cytology in early detection.

Kennedy et al. [17] reported a very high yield in sputum cytology (1.7% prevalence of CIS or invasive carcinoma) in a very high-risk group as part of the University of Colorado...
NCI-sponsored SPORE (Specialized Center of Research Excellence). The subjects in this study had airflow obstruction and at least 40 pack years of smoking histories. This was 17.1-fold the prevalence of such lesions in the Mayo Lung Project. While the Colorado SPORE group represents an excellent cohort for the purposes of acquiring premalignant tissue and evaluating the molecular events of preneoplasia, this population has a very high mortality rate from comorbid conditions (emphysema and cardiovascular disease). Without additional exclusions for comorbidity, this population may be too ill to benefit from screening. Further, the definition of risk groups appropriate for sputum surveillance may be different than that for helical CT screening and should be a focus of future studies.

The NCI Lung Cancer Screening Study at Johns Hopkins found that moderate dysplasia in sputum may result in a 10% future incidence of lung cancer and a 40% severe dysplasia result in future lung cancer [18]. The natural history of CIS is unknown, though a recent study by Vennmans et al. [19] found that five of nine CIS lesions progressed to invasive carcinoma (some in spite of local therapy efforts). Some of these lesions may have been invasive initially but classified CIS due to sampling artifact. It is unknown if some may spontaneously regress.

Many patients in the randomized NCI studies with CIS were treated by aggressive excision, usually lobectomy or pneumonectomy. Later in the study photodynamic therapy was used and was probably helpful in reducing the excess mortality and morbidity associated with pneumonectomy. However, there was no analysis of the Mayo experience linking treatment choices with mortality in the CIS/EHLC cases. It is possible that such treatment tactics lend credibility to the argument that overdiagnosis bias and increased consequent treatment mortality contributed to the failure of screening to reduce mortality with respect to those patients diagnosed because of sputum cytology, but who were radiologically occult. This was not observed in the Bechtel study where the disease-specific mortality was very low. The importance of establishing thoughtful treatment algorithms as part of future screening studies needs to be emphasized.

**History of Autofluorescence Bronchoscopy**

*Kato et al.* [20] addressed the problem of inadequate or delayed localization of superficial bronchial mucosal malignancy by the use of porphyrin injection, followed by bronchoscopic observation using a laser monochromatic light source. Tumor drug-specific fluorescence was detected at 630 nm wavelength, which was distinct from normal tissue fluorescence at 500-580 nm. This technology improved sensitivity. However, photosensitivity reactions and costs were prohibitive when applied to patients without a diagnosis of established lung cancer.

Early approaches by *Palcic, Hung, and Lam* [21, 22] at the British Columbia Cancer Centre in Vancouver, British Columbia, Canada, included dose reduction of porphyrin and in vitro investigations as to optimal excitation wavelengths for distinguishing normal from premalignant and malignant bronchial mucosa. Using blue light at 442 nm from a laser light source, autofluorescence distinctions between malignant and normal mucosa were demonstrated and could be detected in real time using image-intensified cameras. Bronchial epithelial fluorescence was measured in red (630 nm) and green (520 nm). The fluorescence intensities were displayed on a video monitor in real time. Normal bronchial mucosa appears green, while premalignant or malignant tissue appears brown, or brown-red. The demonstration that adequate discrimination of malignant tissue from normal led to the development of the LIFE (Light Imaging Fluorescence Endoscope)-Lung System by Xillix Technologies, Richmond, British Columbia, Canada. Subsequent clinical studies suggested that moderate dysplasia or worse could be localized with marked increase in sensitivity. Enhanced detection of mild dysplasia or metaplasia was not an objective in the development of the system.

**Recent Studies in Autofluorescence Bronchoscopy**

Xillix conducted a seven-site, North American, multicenter study of the device [23] on 173 subjects acquiring 700 biopsies. The study method called for the bronchoscopist to first inspect the central airways with white light and record all suspicious lesions and then to repeat the inspection using fluorescence. The benefit of fluorescence was expressed in terms of relative sensitivity, or the added sensitivity of fluorescence. The relative sensitivity was 2.71 for all lesions. Because the study population included many patients with large visible lesions, a more relevant analysis of those lesions classified as moderate dysplasia, severe dysplasia, or CIS resulted in a relative sensitivity of 6.3. The false-positive rate (.34), however, was quite high in these lesions compared to .10 with white light alone. This study resulted in the approval of LIFE by the U.S. Food and Drug Administration for clinical use.

A study by *Kurie et al.* [24] of 53 subjects enrolled in a chemoprevention trial failed to show increased sensitivity with LIFE. The study group had >20 pack years of smoking but lacked additional risk factors for malignancy such as positive sputum cytology or airflow obstruction. The bronchoscopic evaluation compared biopsies at six predetermined sites to those from sites of abnormal fluorescence. Only 8 (3%) of 245 biopsies showed metaplasia and/or dysplasia and there was a poor correlation with suspicious classification.
by fluorescence. It is likely that the low prevalence of advanced preneoplasia in the study group accounts for the poor performance of the LIFE examination. In addition, most bronchoscopists using the LIFE instrument agree there is a “learning curve” of 20-30 examinations during which the ability to detect abnormal mucosa improves. It may be that in the absence of a high prevalence of abnormality, the learning curve may be longer. With the current specifications, LIFE is not designed to localize lesions with less than moderate dysplasia in severity.

Venmans et al. [25] addressed the issue of possible bias in the North American multicenter study because the order of the examination in the study was white light first, LIFE second. The possible bias effect included improved specificity and/or sensitivity because of the order of the examination. Thus, the design by Venmans et al. randomized the order of the examination with a single bronchoscopist performing the bronchoscopy on 33 high-risk patients. Seventy-one of 139 biopsies were deemed suspicious by the observer. Nine lesions were classified as either moderate or severe dysplasia, or CIS, and four additional lesions showed invasive cancer. Though the number of lesions was small, sensitivity was high in both modalities (89% and 78%, respectively, for LIFE and white light). Specificity was also high for both modalities (61% and 88%, respectively). Only one of the nine preinvasive lesions was classified as moderate dysplasia, however. This may reflect a high threshold of classifying lesions as visibly suspicious, which would tend to reduce yield of high-grade preinvasive lesions and increase specificity, and reduce the relative sensitivity advantage of the LIFE examination.

Kennedy et al. [26] reported results on 55 high-risk subjects undergoing bronchoscopy examinations randomized for both the order of the modality and for two bronchoscopists blinded as to the findings of the other. Fifty-five percent of the subjects had high-grade dysplasia or worse and 78 of 391 biopsies (20%) had high-grade dysplasia or worse. Low-grade (mild) dysplasia or worse was found in 73% of the patients. Only 9% of patients showed no abnormal biopsies. The sensitivity for LIFE in detecting moderate dysplasia or worse by biopsy was 73.1% and 18% for white light. The relative sensitivity was 3.1. The specificity of LIFE, however, was lower than white light, 46% versus 78%. Combined white light and LIFE provided a sensitivity of 80% but a specificity of only 29% [26]. This could be a reflection of a lower threshold of classifying a lesion as visibly suspicious than that demonstrated by Venmans’ group. Some of the differences between these studies reflect marked differences in patient selection and also may reflect variability in histological classification for preneoplasia between institutions. Recently, the histologic typing of lung cancer was revised and clarified [27]. Further, Hirsch et al. have devised an Internet-based, interactive program to help improve and standardize classification of preneoplasia and early lung cancer [28].

Keith et al. [29] at the University of Colorado reported a strong correlation between a histological finding of angiogenic squamous dysplasia and abnormal fluorescence. These preliminary findings raise the possibility that abnormal fluorescence may reflect angiogenic events in tissue. This may explain why many observers have found inflammation in mucosa with abnormal fluorescence one possible explanation for low specificity. Equally important, angiogenesis is likely a key step in the transition of intraepithelial preneoplasia to submucosal invasion. This may be relevant when considering chemoprevention strategies and when considering strategies to improve sensitivity and specificity of endobronchial examinations.

A critically important benefit of these studies is the acquisition of the spectrum of preneoplastic tissue for studies of molecular changes defining the progression to neoplasia but not necessarily reflecting classic histopathologic changes. It is well established that histologically normal appearing bronchial mucosa cells are littered with genetic abnormalities [30]. However, much work is ahead to define the functional and prognostic significance of these changes.

EHLC

It is difficult to estimate the prevalence of central lung cancer, generally squamous cell carcinoma, in a targeted high-risk population. This is because there is an increasing incidence of adenocarcinoma of the lung as well as an increasing size of the smoking female cohort at risk. Seventeen to 29% of lung cancers are squamous cell carcinoma with a 5-year survival rate of 15% [31]. Most of these arise centrally but are discovered either because the patient presents with symptoms of advanced disease and/or because of radiologic findings (hilar masses, atelectasis). In the Mayo Lung Cancer Project, 20% of lung cancers were discovered by sputum cytology when radiologically occult. Similarly, in the study by Kaneko et al. [1], 15 cancers were discovered by spiral CT and three by sputum cytology alone in a study group of 1,369 subjects, mostly males. If this experience can be generalized (3/18, 16.6%) to reflect the expected proportional prevalence of central disease (EHLC), then the order of magnitude of the lung cancer epidemic is such that the volume of EHLC might be 30,000-36,000 new cases per year resulting in 26,00-30,000 deaths in the U.S., similar to that seen in breast cancer (193,700 new cases/42,000 deaths), colorectal cancer (135,400 new cases/57,000 deaths), or prostate cancer (198,100 new cases/32,000 deaths) [31].

In addition, the Kaneko high-risk study population has a yield of positive sputum cytology of 2.2 per 1,000. This is more than respectable in comparison to the yield of
mammograms, occult blood in stool testing sigmoidoscopy or colonoscopy screening, and prostate-specific antigen (PSA) screening, respectively. This yield might be considerably higher in more carefully defined higher risk groups such as those seen in the Colorado SPORE population with a prevalence of 1.7%. We conclude that EHLC represents a highly prevalent, highly mortal epidemic that appears highly treatable in its early stages with low morbidity.

The Problem of Specificity

The low specificity of fluorescence is problematic in that more biopsies may need evaluation at greater cost and more biopsies may tend to result in longer examinations and more bronchitis secondary to the procedure. Episodes of bronchitis after evaluation have been generally minor but occasionally have been associated with exacerbations of reactive airways disease enough to result in hospitalization. The high sensitivity and low specificity of fluorescence bronchoscopy are similar to other imaging modalities such as CT in the diagnosis of small malignant lung nodules [2]. High sensitivity and low specificity also characterize other cancer screening tools such as occult blood testing, mammography, and PSA.

Endobronchial ultrasonography may be a helpful adjunct to identify mucosal wall thickening, which may be useful in distinguishing CIS from more invasive disease, thus improving specificity for invasive cancer. Ultrasound would not likely be helpful in avoiding false-positive biopsies for dysplasia, however. Quantitative fluorescence imaging or combined fluorescence-reflectance imaging may also be helpful in future bronchoscopic devices to address specificity.

The Current Value of LIFE Technology

Clearly LIFE technology is of great value in acquiring tissue for molecular biology studies of lung carcinogenesis. It also appears to be of value in conducting chemoprevention trials by locating and monitoring areas of field cancerization during intervention of preneoplasia. In chemoprevention trials, it has been noticed that a previous biopsy site may have persistent abnormal fluorescence characteristics several months to several years later. Bronchoscopists conducting trials based on subsequent biopsy samples will find it relatively easy to find the previous sites but difficult to interpret changes in fluorescence unless the original area was extensive. Limited experience also suggests some small sites of preneoplasia or CIS may be removed by the biopsy procedure, confounding the evaluation of study chemoprevention agents [26, 32].

The fluorescence bronchoscopy technology may be of value in detecting subtle synchronous malignancy in preoperative lung cancer patients as well as perhaps more accurately estimating the extent of cancer prior to resection. The technology may be of value in monitoring patients undergoing local therapies for EHLC.

While the above potential clinical and research uses are important, examination of expectorated sputum remains the best hope for identifying patients most likely to benefit from fluorescence bronchoscopy. Improving sensitivity of sputum, enough to justify its widespread use in the appropriately defined risk group, is essential if fluorescence bronchoscopy is to make the transition from an effective research tool, which it is, to an important clinical tool for reduction of lung cancer mortality.

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References


