DIFFERENTIAL DIAGNOSIS

Current Attributes :
1) Cough, chronic
2) Weight loss

There are 33 related Conditions with minimum 2 findings matched.

Infectious - Agent Specific

1,2 Immune deficiency , acquired (AIDS/HIV) (ICD 042) ***
1,2 Tuberculosis (ICD 011.9) ***
1,2 Actinomycosis, thoracic (ICD 039.1)**
1,2 Blastomycosis (ICD 116.0) **
1,2 Coccidioidomycosis, pulmonary, chronic (ICD 114.4) **
1,2 Histoplasmosis, pulmonary (ICD 115.05) **
1,2 Nocardiosis, pulmonary (ICD 039.1)**
1,2 Paracoccidiodomycosis (S.A. Blastomyco) **
1,2 Tuberculosis pulmonary **
1,2 Tuberculosis, cavitary pulmonary (ICD 011.20) **

Infected Organ - Abscess

1,2 Bronchiectasis (ICD 494) ***
1,2 Bronchiolitis obliterans **
1,2 Lung abscess (ICD 513.0) **
1,2 Middle lobe syndrome (ICD 518.0) **

Granulomatous - Inflammatory

1,2 Sarcoidosis (ICD 135) **
1,2 Wegeners granulomatosis (ICD 446.4) **
1,2 Wegener's pulmonary (isolated) disease (ICD 446.4) **

Neoplastic

1,2 Metastatic lung disease (ICD 197.0) ***
1,2 Metastatic lung lymphatics/carcinoma (ICD 162.9) ***
1,2 Adenocarcinoma, bronchial (ICD 162.9) **
1,2 Carcinoma lung squamous cell/large cell (ICD 162.9) **
1,2 Carcinoma, bronchogenic (ICD 162.9 primary - 212.3 benign) **
1,2 Carcinoma, laryngeal (ICD 161.9) **
1,2 Carcinoma, oat cell (small cell), lung (ICD 162.9) **
1,2 Pulmonary lymphoma (ICD 162.9 - 212.3 benign) **
1,2 Hypereosinophilic syndrome (ICD 288.3) *

Allergic - Collagen - Auto-Immune

1,2 Pneumonia, eosinophilic, prolonged (ICD 518.3) **
1,2 Maple bark stripper lung/disease (ICD 495.6) *

Hereditary - Familial - Genetic

1,2 Cystic fibrosis (mucoviscidosis) (ICD277.01) **
1,2 Severe combined immunodeficiency synd (ICD 279.2) *

Reference To Organ System

1,2 Emphysema/COPD/Chronic lung disease (ICD 496 unspecified - 491.20 chronic bronchitis) ***
1,2 Pulmonary alveolar proteinosis (ICD 516.0) **

Poison - Agent Specific

1,2 Berylliosis (ICD 503) **

Others

1,2 Achalasia
1,2 Idiopathic Pulmonary fibrosis
1,2 Parasitic infestations, especially strogyloidiasis
1,2 Whooping cough

MEDICAL PROCEDURE

FLUORESCENCE BRONCHOSCOPY

Elizabeth Passalidou, MD
Jeremy George, MD

Fluorescence bronchoscopy, one of several new initiatives in the field of early lung cancer detection, is currently being evaluated as a method for detecting dysplasia, carcinoma in situ, and early microinvasive carcinoma involving the large airways. This article will review recent developments in this area and consider the possible role of this technique in lung cancer management. General issues related to lung cancer screening are presented separately.

Rationale

It is generally accepted that the poor prognosis of lung cancer is due largely to the late clinical presentation of the disease. Although surgery for early stage tumors provides the best prospect of cure, the majority of patients (80 percent) already have advanced and inoperable disease when they present to their physicians [1,2]. An obvious approach is to develop sensitive methods for detecting lung cancer at much earlier stages when treatment is more likely to be curative.

It has been appreciated since the publication of postmortem studies in the 1950s that preinvasive changes involving the bronchial epithelium may occur over wide areas of the tracheobronchial tree and that such changes are particularly common in individuals who have smoked heavily and/or developed other sites of invasive lung cancer [3,4]. These observations underlie the widely held belief that lung cancer, particularly squamous cell carcinoma, develops through a series of morphological stages from metaplasia, to dysplasia, to carcinoma in situ, and then to invasive disease.

The possibility of detecting preinvasive and early invasive carcinoma was raised by a longitudinal study of sputum obtained from uranium miners in whom abnormal epithelial cells were found several years before a clinical diagnosis of lung cancer was established [5]. However, three large trials sponsored by the National Cancer Institute subsequently failed to demonstrate a significant reduction in lung cancer mortality in patients who had undergone intensive screening with sputum cytology [6-11].

Although sputum cytology failed to detect the majority of lung cancers and influence overall mortality in screened versus unscreened groups, it succeeded in identifying a small number of patients with carcinoma in situ and radiologically occult squamous cell carcinoma involving the central airways. The bronchoscopic localization of these early lesions proved particularly difficult but was ultimately judged to be worthwhile because surgical resection was associated with excellent 5-year survival in the range of 90 percent [12,13].

Although screening with sputum cytology is not currently recommended by any major advisory organization, interest in its use is returning because of technical advances which potentially could enhance the sensitivity of the technique. As examples, the identification of a number of molecular markers of malignancy and the development of computer-assisted image analysis of exfoliated cells have the potential to detect early lesions more reliably than visual examination alone [14]. Preliminary studies involving archived sputum samples, where the eventual clinical outcome is already known, have shown that the use of molecular genetic and immunocytochemical markers may enable abnormal cells to be detected up to 1 to 2 years before the actual malignant diagnosis was established using conventional tests [15,16].

However, if enhanced detection with sputum cytology is successful in detecting in situ lesions, the practical difficulty of locating them bronchoscopically remains. In an attempt to address this problem, a number of bronchoscopic devices have now been developed which exploit differences in the fluorescence properties of normal and abnormal bronchial epithelium.

Instrumentation

It has been known since the early part of this century that tissues fluoresce when exposed to light of a suitable wavelength and that infiltrating tumours, by disturbing these properties of fluorescence, could be detected more easily [17,18]. However, the intensity of fluorescence was often too low to be detected with the naked eye or was swamped by reflected light from the excitation beam. Interest was therefore directed to the use of exogenous fluorescent compounds, such as hematoporphyrin derivatives, which were retained by malignant tissues with some selectivity and which produced characteristic and more intense fluorescence images when exposed to light of a suitable wavelength [19,20]. The usefulness of this technique for general diagnostic purposes was severely limited by transient but severe photosensitivity of the skin caused by the photosensitizer.

Interest in autofluorescence has returned because of the development of a number of imaging techniques that permit the detection of subtle differences in fluorescence characteristics. Observations in the lung have shown that dysplasia, carcinoma in situ, and microinvasive carcinoma exhibit slightly weaker red fluorescence but much weaker green fluorescence than normal tissues when illuminated by blue light [21]. The reasons for this difference are not fully understood but may be due to increased epithelial thickness in association with increased blood flow and a reduced concentration of fluorophers within the abnormal tissue [22,23].

Several bronchoscopy systems are commercially available which exploit this difference in red and green fluorescence. The best known is the light-induced fluorescence endoscopy (LIFE) device (Xillix Technologies Corporation, Vancouver, Canada) [24,25].

The bronchial tree is illuminated by blue (442 nm) light from a helium-cadmium laser, and the fluorescence images are collected by the imaging bundles of the bronchoscope. The red and green wavelengths are filtered and amplified with separate image-intensifying cameras. Their relative intensities are then measured and used to create a computer-enhanced image, which delineates the abnormal areas of fluorescence when displayed on a monitor. Fluorescence bronchoscopy is performed during the same session as white light bronchoscopy, using separate light sources.

More recently, Karl Storz, in conjunction with the Laser Research Institute in Munich, has developed a system that enables differences in tissue fluorescence to be detected using a conventional xenon light source, together with an optical filter fitted to the eyepiece of the bronchoscope [26]. The light source has the capability of illuminating the bronchial tree with white light and two bands of blue light (380 to 460 nm and 380 to 440 nm), the mode of illumination being controlled by a switch incorporated into the bronchoscope. The optical filter transmits red and green wavelengths together with a small part of the excitation wavelength, allowing visualization in areas of low fluorescence. The images may be viewed directly through the eyepiece of the bronchoscope or displayed on a monitor using a sensitive camera.

The Storz system is designed to detect both autofluorescence and fluorescence induced by administering the pro-drug 5 amino-levulinic acid (ALA) [27,28]. ALA administration results in the production of porphyrin precursors to heme, particularly protoporphyrin IX, which accumulate preferentially in areas of dysplasia, carcinoma in situ, and invasive carcinoma [29]. Illumination of the bronchial tree with the narrower band of blue light (380 to 440 nm) three hours after ALA administration leads to increased red fluorescence within abnormal tissues while green fluorescence remains low, thereby enhancing the contrast between normal and abnormal areas [27,28]. Although ALA may be administered orally, it is often applied topically by nebulizer to minimize possible systemic side effects.

Autofluorescence with the Storz system is visualized by illuminating the bronchial tree with the broad band of blue light (380 to 460 nm). Normal bronchial epithelium appears greyish-blue, while abnormal epithelium appears reddish-brown when viewed through the filter. Although comparative studies between autofluorescence and ALA-induced fluorescence have not been conducted, autofluorescence is currently the preferred technique, as it is simple and easy to perform. As with the LIFE device, fluorescence bronchoscopy is performed during the same session as white light bronchoscopy.

Clinical Experience

Most of the published clinical studies on fluorescence bronchoscopy have been conducted with the LIFE device. In the majority, white light bronchoscopy has been performed before fluorescence bronchoscopy in the same session, and the abnormal areas observed with each modality have been carefully documented. The ability to detect preinvasive changes and invasive carcinoma has then been assessed by a histological examination of the biopsies taken from these abnormal areas.

The four largest studies involving the LIFE device have reported a 1.5 to 6.3-fold increase in the detection of dysplasia and carcinoma in situ [24,25,30,31]. Although invasive carcinomas are relatively easy to detect with white light bronchoscopy, one of these studies has also reported improved detection of these lesions with fluorescence bronchoscopy [30]. However, the design of these studies has been criticized because performing a preliminary white light bronchoscopy may lead to bias in sensitivity of the subsequent fluorescence bronchoscopy [32,33]. In addition, the study that showed the largest advantage for fluorescence bronchoscopy reported results that were based upon the number of biopsies that revealed abnormal histology, rather than upon the number of discrete lesions detected [30,33]. The ability to ascertain an abnormality may therefore have been exaggerated if more than one biopsy was taken from a discrete lesion. Although these criticisms should be taken into account when interpreting the data, the broad agreement that exists among these large studies suggests that fluorescence bronchoscopy with the LIFE device genuinely facilitates the detection of dysplasia and carcinoma in situ.

However, data in favor of fluorescence bronchoscopy have not been universal. As an example, a 1998 study from the MD Anderson Cancer Center found a lower sensitivity associated with the LIFE device [34]. The authors of this study had hoped that the LIFE device would facilitate the detection of metaplasia and dysplasia, which were endpoints in their lung cancer chemoprevention trials. However, the detection of these abnormalities was not significantly increased in 39 individuals undergoing combined white light and fluorescence bronchoscopy when compared with the results obtained in a matched group of 53 controls undergoing white light bronchoscopy alone. Biopsies from areas judged to be normal by the LIFE device yielded a similar number of metaplastic and dysplastic lesions as did those from areas judged to be abnormal. The data obtained with the LIFE device were stratified according to smoking status and history of previous smoking-related cancer, in order to establish whether abnormalities of fluorescence might reflect lung cancer risk factors other than histological abnormalities, but no correlations were found.

The apparent discrepancy between the findings of the MD Anderson study and other studies involving the LIFE device has been attributed to the lower prevalence of severe dysplasia and absence of carcinoma in situ in participants recruited into the MD Anderson study [35]. It has therefore been suggested that the LIFE device has sufficient sensitivity to detect severe

dysplasia and carcinoma in situ but is incapable of detecting milder degrees of dysplasia and metaplasia[35].

Clinical experience with the Storz fluorescence bronchoscope is not as extensive as with the LIFE device. Two preliminary studies have shown a 1.7 and 1.4-fold improvement in the rate of detection of dysplasia and carcinoma in situ with autofluorescence and ALA-induced fluorescence, respectively, when compared with white light bronchoscopy [28,33]. A large multicenter study comparing autofluorescence with white light bronchoscopy is currently in progress in Europe. The study design differs from the majority of previous investigations, in that participants are being randomised to undergo either white light bronchoscopy alone or white light bronchoscopy in combination with autofluorescence bronchoscopy [33]. The data will be expressed according to the number of discrete lesions rather than abnormal biopsies.

An important limitation of fluorescence bronchoscopy is the high rate of false positive findings. In a large multicenter study, only 95 of 285 biopsies obtained from areas with abnormal fluorescence detected by the LIFE device actually contained abnormal histology, yielding a positive predictive value of only 33 percent [30]. However, it has been suggested that up to 50 percent of the histologically false positive biopsies may still carry molecular genetic lesions associated with malignancy despite their normal appearance on light microscopy [36].

Optimal Use

The ability to detect dysplasia and carcinoma in situ with fluorescence bronchoscopy raises the important clinical question as to how these lesions should be managed. Although the lesions are widely thought to be premalignant, large longitudinal studies that might confirm this hypothesis have not been undertaken due to the previous difficulty identifying these lesions with white light bronchoscopy. Review of the literature reveals only 4 patients in whom progression from a preinvasive stage to invasive carcinoma has actually been documented histologically [37,38].

In some centers in Japan and the United States, carcinoma in situ has been managed with surgery and/or photodynamic therapy (PDT) [13,39,40]. Although follow-up studies of patients undergoing surgery have revealed excellent 5-year survival, they also have shown a relatively high risk (5 percent per year) of developing subsequent new lung cancers which, in some cases, could not be managed with further surgery due to reduced respiratory reserve [13]. Concerns have therefore been expressed that such aggressive treatment for preinvasive lesions is unjustified when there is no certainty that some or all will progress to invasive disease, particularly when the risk of developing a subsequent invasive lung cancer is so high [41].

Careful surveillance with fluorescence bronchoscopy is now feasible, so that it should be possible to intervene with surgery or PDT if and when the lesion becomes invasive. The advantage of this approach is that it should provide information on the natural history of these early lesions. Molecular genetic studies are now providing important insights into the development of malignancy [42,43]. Longitudinal studies of patients with dysplasia and carcinoma in situ should provide samples for comparing genetic differences (and differences in gene expression) at different stages and may enable markers of tumor progression to be identified. Ultimately, such markers could be used to identify the early lesions that are destined to become invasive and thus warrant immediate treatment.

Fluorescence bronchoscopy is clearly too invasive, expensive, and time-consuming to be used to screen all populations at risk of lung cancer. Its success therefore depends upon the parallel development of sensitive primary screening tests, which would prompt fluorescence bronchoscopy if a positive result were found. Recent developments in sputum cytology may lead to improved sensitivity; alternatively, the demonstration of specific volatile organic compounds in the breath of lung cancer patients offers encouragement that noninvasive screening tools other than cytology may soon become available [14,44].

Fluorescence bronchoscopy can only be used to detect lesions within the large airways. Early detection strategies will therefore need to include sensitive methods for locating peripheral lesions. Although it is widely accepted that the chest x-ray lacks sufficient sensitivity for this purpose, preliminary experience with low dose helical computed tomography has been encouraging and offers hope that this technique may complement sputum screening and fluorescence bronchoscopy[45-47].

Conclusion

Fluorescence bronchoscopy promises to provide valuable insights into the natural history of preinvasive bronchial epithelial lesions and early invasive lung cancers involving the central airways. If sensitive primary screening tests and reliable markers of tumor progression can be developed, the technique may become a very powerful clinical tool. However, it will ultimately be necessary to demonstrate that the use of these new tools is associated with a significant reduction in lung cancer mortality before integration of fluorescence bronchoscopy into a screening strategy for lung cancer can be recommended.

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