

Fluorescence bronchoscopy for the early detection of lung cancer

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Fluorescence bronchoscopy is currently being developed as a method for detecting early lung cancers, carcinoma in situ, and dysplastic lesions of the tracheobronchial tree. The ultimate aim is to detect pre-invasive neoplastic lesions and eradicate them before they have become invasive.¹ This proactive approach is one of several new strategies that are being developed to detect lung cancers at early stages when treatment is more likely to be curative. This review will therefore describe recent developments in fluorescence bronchoscopy and consider the possible impact of this new technique on the management of lung cancer.

The rationale for early lung cancer detection

Lung cancer accounts for more deaths than any other malignancy in the developed countries of the world. Although surgery offers the best prospect of cure for patients with early stage tumours,² the majority already have advanced and inoperable disease by the time they develop symptoms and present to their general practitioners.³ The five year survival rates for patients with lung cancer have remained depressingly low at 7-13%.^{4, 5}

These poor figures have been explained by considering the natural history of the disease.⁶ On the assumption that lung cancers have an exponential pattern of growth, it has been estimated that a tumour of 1 cm in diameter, which is the smallest lesion that can be detected on a plain chest radiograph, will have undergone 30 volume doublings. A rapidly growing tumour such as a small cell carcinoma may take 2.4 years to achieve this size while a non-small cell carcinoma may take 7-13 years. Plenty of time will therefore have elapsed for metastatic spread to develop before the tumour is diagnosed and treated. An obvious approach to this problem is to develop methods for detecting lung cancers at very much earlier stages when treatment is more likely to be curative.

It has been known since the studies of Auerbach and colleagues that changes of metaplasia, dysplasia and carcinoma in situ may occur over wide areas of the tracheobronchial tree and that they are particularly common in individuals who have smoked heavily and/or developed invasive lung cancer.^{7, 8} These observations have led to the widely held belief that lung cancers develop through a series of morphological changes from metaplasia to dysplasia to carcinoma in situ and then to invasive disease.

The possibility of detecting these pre-invasive lesions by cytological study of the sputum was raised by the findings of a longitudinal

study of radium workers in whom abnormal epithelial cells were found years before a clinical diagnosis of lung cancer was made.⁹ However, a multicentre trial conducted at the Mayo Clinic,¹⁰ Johns Hopkins Hospital,¹¹ and Memorial Sloane-Kettering Hospital¹² failed to demonstrate improved long term survival in patients who had undergone intensive screening with sputum cytology.¹³⁻¹⁵ Although more cases of early stage lung cancers were detected in the screened populations with improved five year survivals, this was attributed to lead time bias as the eventual mortality from lung cancer was identical to that of the control groups.¹³⁻¹⁵

Despite the disappointment of this trial, interest has continued in the development of sputum cytology as a screening tool by the use of immunocytochemical¹⁶ and molecular genetic¹⁷ tumour markers and there is evidence to suggest that its sensitivity may be enhanced significantly. However, the visualisation of early lesions within the tracheobronchial tree by conventional bronchoscopy may be technically very difficult as they may be only a few cell layers thick and a few millimetres in surface diameter. For example, the systematic studies of Auerbach *et al* demonstrated carcinoma in situ in 15% of the microscopic sections from the tracheobronchial trees of patients dying from invasive lung cancers,⁸ yet these changes are seldom if ever observed at a routine fiberoptic bronchoscopic examination. In order to facilitate the detection of these lesions, bronchoscopic systems are now being developed that exploit differences in the fluorescence properties of normal and abnormal bronchial mucosa.

Development of fluorescence imaging

It has been known since the early part of this century that tissues have the ability to fluoresce when exposed to light of a suitable wavelength. The diagnostic potential of tissue fluorescence became apparent when it was noted that infiltrating tumours disturbed the normal fluorescence characteristics of a particular tissue. For example, ultraviolet light from a Wood's light was used in the 1930s and 1940s to differentiate tumour from surrounding normal tissues in specimens obtained from the gastrointestinal tract, breast, and skin.^{18, 19}

A particular practical disadvantage of autofluorescence was that the colour of the fluorescence image was variable and its intensity was often too low to detect with the naked eye. Interest was therefore directed to the use of exogenous fluorescent compounds that were selectively retained by malignant tissues and which produced characteristic and more

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intense fluorescence images when exposed to ultraviolet light. In 1960 Lipson and Baldes reported on the use of a derivative of haematoporphyrin (HpD) to induce a distinct red fluorescence in a number of malignant lesions.²⁰ The important disadvantage of HpD, however, was that it caused transient light sensitivity of the skin and, although it has considerable therapeutic potential in photodynamic therapy today, its diagnostic value is more limited.

Interest in the use of autofluorescence as a diagnostic tool has returned with the development of image intensifying cameras and computer enhanced imaging that enable quite subtle differences in fluorescence to be demonstrated. Observations in the lung have shown that dysplasia, carcinoma in situ, and microinvasive carcinomas exhibit slightly weaker red fluorescence but much weaker green fluorescence than normal tissues when illuminated by blue light.²¹

The best known fluorescence bronchoscope that employs this principle is the lung imaging fluorescence endoscopy (LIFE) device which has been developed by Dr Steven Lam's group in conjunction with Xillix Technologies Corporation of Vancouver.²²⁻²³ The bronchial tree is illuminated by blue light (442 nm) from a helium-cadmium laser and the fluorescence images are collected by the imaging bundles of the bronchoscope, filtered into their separate wavelengths, and the intensities of the red and green wavelengths measured. Using an image intensified camera and mathematical transformation (a non-linear discriminant function combination of the red and green intensity values), a computer enhanced pseudo image is created allowing the delineation of abnormal areas when displayed on a monitor.

The theoretical disadvantage of a system that uses image intensifying cameras and computer enhanced imaging is the amplification of background noise and consequent loss of specificity. Other devices are being developed, however, which do not require image intensifying cameras. For example, Stepp and colleagues are developing a system, in collaboration with Karl Storz of Germany, that enables fluorescence images to be visualised with the use of optical filters built into the bronchoscope.²⁴ Discrimination with the Storz bronchoscope may be enhanced further by inducing fluorescence with 5-amino-laevulinic acid (ALA).²⁴⁻²⁵ Administration of ALA results in an accumulation of porphyrin precursors to haem, particularly protoporphyrin IX, which exhibits strong red fluorescence and which accumulates preferentially in dysplasia, carcinoma in situ, and invasive carcinomas.²⁶ Illumination of the bronchial tree with blue light three hours after administration of ALA leads to increased red fluorescence within abnormal tissues while green fluorescence remains low, thereby enhancing the contrast between normal and abnormal areas.²⁴⁻²⁵ Although ALA may be administered orally, it is given topically by nebuliser to minimise any possible systemic side effects.²⁴⁻²⁵ It is therefore very much more suited for diagnostic work than HpD.

Clinical experience with fluorescence bronchoscopy

Virtually all of the published clinical data on fluorescence bronchoscopy have been acquired with the LIFE device. In most of these studies 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.²²⁻²³ The ability of each modality to detect dysplasia and carcinoma in situ has then been assessed by a histological examination of the biopsy specimens taken from these abnormal areas.

Preliminary experience obtained by Dr Lam's group showed that fluorescence bronchoscopy enhanced the detection of dysplasia and carcinoma in situ by approximately 50%.²²⁻²³ In a more recently published study of 173 subjects conducted at seven institutions in the USA and Canada the detection of moderate to severe dysplasia and carcinoma in situ was found to be 6.3 times greater with fluorescence bronchoscopy than with white light bronchoscopy.²⁷ However, inspection of the data from this study reveals that only 95 of 285 (33%) biopsy specimens obtained from areas judged to have abnormal fluorescence actually had an abnormal histological appearance, suggesting a very low specificity.

It has been suggested that the low specificity of the LIFE device may be overestimated as it is thought possible that up to 50% of the "false positive" biopsy specimens carry molecular genetic lesions associated with malignancy despite their normal histological appearance.¹ However, a recently published study from the MD Anderson Cancer Centre has cast serious doubt on the sensitivity of the LIFE device.²⁸

The design of the MD Anderson study differed from previous studies in that the results obtained with the LIFE device, using both white light and fluorescence bronchoscopy, were compared with those obtained with white light bronchoscopy alone in a matched group of controls.²⁸ The authors had hoped that the LIFE device would facilitate the detection of metaplasia and dysplasia as these were study end points in their lung cancer chemoprevention trials. However, the detection of these abnormalities was not significantly increased in the LIFE group. It was also found that biopsy specimens from areas judged to be normal by the LIFE device yielded a similar number of metaplastic and dysplastic lesions as areas judged to be abnormal. To establish whether abnormalities of fluorescence might reflect risk factors for lung cancer other than histological abnormalities, the data obtained with the LIFE device were stratified according to smoking status and histories of previous smoking related cancers 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.²⁹ It therefore seems likely 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.²⁹

It should be appreciated that fluorescence bronchoscopy is at an early stage in its development and it is likely that the sensitivity and specificity of future systems will improve significantly as the technology advances. It should also be appreciated that the mechanisms underlying tissue fluorescence are incompletely understood and that further improvement in imaging devices should occur as the science develops. Possible technological developments include the use of exogenous fluorescent compounds with more acceptable toxicity, multiple excitation and emission wavelengths, and the design of systems using pulsed light with gated detectors which will allow simultaneous white light and fluorescence imaging.³⁰

Role of fluorescence bronchoscopy in management of lung cancer

The ability to detect metaplasia, dysplasia, and carcinoma in situ within the tracheobronchial tree raises the important clinical question as to how these lesions should be managed. In the USA and Japan carcinoma in situ has been managed with surgery³¹ and photodynamic therapy.³² However, concerns might legitimately be expressed that such aggressive treatment is unjustified when there is no certainty that some or all of these lesions will progress to invasive disease.

It is therefore essential that we develop an understanding of the early lesions that are destined to become malignant. Molecular genetic studies are now providing important insights into the development of malignancy.³³⁻³⁴ Longitudinal studies of patients with metaplasia, dysplasia, and carcinoma in situ involving the tracheobronchial tree are likely to be of great value as they will provide samples for comparing genetic differences (and differences in gene expression) at different stages and may enable markers of tumour progression to be identified. Ultimately, such markers could enable decisions to be made as to which early lesions are likely to become invasive and thus warrant treatment.

It is also important that we evaluate the treatment of early lesions in carefully controlled clinical trials. The detection and treatment of pre-invasive lesions will be extremely laborious and costly and it will be necessary to demonstrate that this strategy results in a significant reduction in lung cancer mortality. Large multi-centre trials with prolonged follow up, that make allowances for lead time bias, will be needed to answer this question.

Conclusions

Fluorescence bronchoscopy is at an early stage in its development. Although its specificity and sensitivity may currently be questioned,²⁸⁻²⁹ it clearly has the potential to enhance the detection of severe dysplasia and carcinoma in situ. At present little is known of the natural history of these lesions and, in particular, their risks of

progressing to invasive carcinoma. If systems can be developed which allow metaplasia, dysplasia, and carcinoma in situ to be detected reliably, fluorescence bronchoscopy may prove to be a very valuable research tool by facilitating longitudinal studies of patients with these lesions.

It remains to be seen, however, whether fluorescence bronchoscopy will become a valuable clinical tool. In the UK we will need to see evidence that "pre-invasive lesions" progress to invasive malignancy and that their eradication leads to a significant reduction in lung cancer mortality.

New strategies are needed if we are to improve the outlook for lung cancer patients. Although previous attempts to detect and treat lung cancers at early stages have failed, we should welcome this new initiative by supporting carefully controlled trials. At the very least, we will gain valuable insights into the natural history of this common and lethal disease.

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