Solunum 3, Özel Sayı 2:171-173, 2001

# THE EARLY DIAGNOSIS AND TREATMENT OF LUNG CANCER

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In the United Kingdom, lung cancer accounts for around 23% of all cancer deaths. In 1997 it was responsible for nearly 35,000 deaths. It is the commonest cause of cancer death in men and in 1999 superseded breast cancer as the commonest cause in women, a striking illustration of the greater success achieved in the detection and effective treatment of breast cancer. In contrast, there has been little or no change in the overall mortality from lung cancer in the past three decades. National trends indicate a slight decrease in male lung cancer but a significant increase in female lung cancer, reflecting the change in patterns of tobacco consumption in men and women since the 1940's. Most patients present with advanced disease and have a poor prognosis. In Manchester, the five year survival for all cases diagnosed between 1990 and 1992 was only 5.4%.

Efforts have rightly been directed at smoking prevention and cessation. Whatever the success of these interventions, lung cancer in smokers and ex-smokers is certain to continue to pose a major problem for society for several decades to come.

In the U.K., there has until recently been an extraordinary neglect of a cancer which is preventable, predictable and, if diagnosed at an early stage, eminently treatable. Surgery remains the best therapeutic option for cure, but only 10% of patients are suitable for surgery at the time of initial presentation. Five year survival is closely linked to tumour stage, ranging from over 70% in Stage IA disease, through 55% for Stage I, 25% for Stage II and 20% for Stage IIIA disease.

## EARLY SCREENING EXPERIENCE

These figures demonstrate the need for early detection and treatment if lung cancer is to be cured. However, early experience with lung cancer screening, using chest radiography and/or sputum cytology, failed to show any apparent beneficial effect on mortality. These include 4 randomised controlled studies, three in the U.S.A., the best known being the Mayo Clinic Project, in which nearly 11,000 male smokers over the age of 45 were randomised to four-monthly or annual chest radiographs and sputum cytology. Patients in the screened group showed improved staging and resectability with improved survival and fatality rates. There was no reduction in mortality for the whole group, indeed it was slightly higher due to an apparent increased incidence of lung cancer in the screened group. The study has been criticised however, in a number of respects; the study was under-powered, only able to detect 50% reduction in mortality; the screened population was arguably too broad; the controlled group was "contaminated" in that over 50% of patients in the group underwent additional chest radiography during the study period; the overall rate of adherence to trial protocol was only 75% in the screened group and 50% in the controlled group. Finally, the assessment of cumulative mortality at 9 years is now considered sub-optimal to assess the efficacy of the trial, assessment at 3 - 7 years from baseline screening considered more suitable. Adjusting for these potential sources of inaccuracy yields a possible mortality improvement from radiographic screening that could be as high as 43%. The current position regarding this and other early studies is that they cannot be regarded as definitive evidence against the benefits of screening. The tumours detected in these studies were twice as likely to be resectable, with a consequent improvement in five year survival.

Allowance must be made, in the assessment of screening results, for a number of potential confounding factors. These include lead-time bias (advancing the time of diagnosis rather than moving back the time of death), length-time bias (the detection of less virulent tumours), and over-diagnosis (the detection of biologically insignificant tumours which would not have become apparent during the patient's lifetime). There is however good evidence from patients who either refused, or were unfit for, surgery, that untreated Stage I lung cancer has a dismal prognosis, with 5 year survival of only 5 -10%. **Epigrammatically, "Detect, Resect" must be the aim.**

## IDENTIFIATION OF HIGH-RISK GROUPS

Even if one accepts the results of the Mayo Clinic and other early studies at face value, the conclusions are in contradiction to the clear evidence that diagnosis at an earlier stage improves survival. This must mean that too few cancers were detected, and points to the need to refine surveillance and investigation in the direction of higher-risk groups. At the simplest level, this could mean older patients with a heavier smoking history. At

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the further end of the risk scale, it is possible to identify groups of patients in whom lung cancer is the commonest single cause of death. These include survivors from treated head and neck cancer, patients with asbestosis (especially if smokers), and elderly smokers with airflow limitation. It is not widely appreciated that measurable airflow obstruction is an independent risk factor for lung cancer. An American lung health study of 6,000 smokers with airflow limitation found that lung cancer was the commonest cause of death at the end of five years, exceeding heart disease and stroke.

## GENETIC PREDISPOSITION TO LUNG CANCER

Considerable attention has been paid in recent years to the detection of molecular and genetic abnormalities predisposing to sequential malignant change in the bronchial epithelium, the so-called "genetic cascade". One example is the mutation and inactivation of suppressor genes, the most well known of which is p53, acting as "the guardian of the Genome" blocking the cell cycle when there is DNA damage and promoting apoptosis, these functions lost in the mutated form. p53 mutations and protein over-expression can be demonstrated not only in frank malignancy but in the non-cancerous mucosa of cancer patients. Other suppressor genes include p16, inactivated by hyper-methylation, and the fragile histidine triad site on the short arm of chromosome 3, which is subject to deletions in cancerous and pre-cancerous lesions.
A second important group of genetic abnormalities is the mutation, de-regulation or over-expression of Oncogenes. Examples include K-ras mutation which may be important for the activation of adeno-carcinoma, Cyclin D1 and c-myc over- expression, seen in up to half of non-small cell lung cancers and dysplasias, and hnRnpa2/b1, a ribonuclear protein found to be over-expressed in cancer cell lines and dysplasias and a potential marker for likelihood of progression to invasive cancer in exfoliated epithelial cells.
A third genetic phenomenon of potential importance is Loss of Heterozygosity, especially 3p deletions from the short arm of chromosome 3, a frequent and early genetic alteration in bronchial epithelium; loss of alleles is also demonstable in areas of dysplasia adjacent to cancerous change. Deletions have also been observed on 8p,9p and 5q. The number and extent of allele deletions could predict the rate of disease progression. The study of gene expression in bronchial epithelial cells requires the development of gene probe assays capable of assessing the mutational status of a large number of candidate genes. The application of such techniques to population-based screening is far from practical at the present time. Options for future therapy include the replacement of mutated genes, a technique already attempted using the intra-tumour injection of p53 packaged in a retroviral vector, found to induce tumour regression in advanced carcinoma. Clearly the potential de-ciphering of other molecular targets will progressively increase therapeutic possibilities.

## DNA DAMAGE AND REPAIR

The mechanism for DNA damage and repair is largely enzymic, and is thus capable of study by enzyme assay. We have used DNA, extracted from bronchial washings and brushings and amplified by PCR, to look at polymorphisms in certain enzyme systems and their potential for altering the response to tobacco-related carcinogens including nitrosamines and polycyclic aromatic hydrocarbons. We have found, for example, that the null genotype for one of the glutathiones-S-transferases, GTSM1, is seen with increased frequency in adeno-carcinoma but with decreased frequency in squamous and small cell lung cancer in comparison with controls, suggesting that different carcinogens may be important in the carcinogenesis of the two types. Patients with a variant genotype for the enzyme quinone oxidoreductase, exhibiting only 2% of the wild-type protein, were found to have a five-fold increase in risk of small cell lung cancer (odd ratio 4.9), rising to nearly 10% (odds ratio 9.7) in heavy smokers. This clearly suggests that this enzyme is important in the detoxification of carcinogens responsible for small cell tumours, probably benzo(a)pyrine metabolites.

## NEW CLINICAL INVESTIGATION METHODS

The use of epidemiological information, combined with techniques for identifying bio-markers, appears capable of defining a group of risk factors which can be used to identify patients at high risk of lung cancer, either individually or for population-based study. The question then arises as to whether we now have sufficiently sensitive detection techniques, and treatments for early lesions of sufficient efficacy, to make a real impact on lung cancer mortality. Techniques under scrutiny include, still, sputum cytology, low-dose CT scanning and fluorescence bronchoscopy.

## SPUTUM CYTOLOGY

Sputum cytology as originally developed is relatively insensitive labour intensive, though still highly specific. Its sensitivity may be improved by the immune staining of transformed epithelial cells and by PCR based assays to detect oncogene mutation. The detection of so called Malignancy-Associated Changes in the morphology and distribution of DNA in the nuclei of "normal" cells in the vicinity of malignancy may also improve the detection rate. The use of automated sputum cytology renders the detection of morphological changes in exfolliated cells a more practical proposition for a population-based screening programme.

## CT SCANNING

The detection of peripheral-type early carcinomas requires the use of imaging techniques, chest radiography being increasingly superseded by low-dose helical CT scanning, enabling the entire thorax to be examined during a single breath-hold of around 20 seconds. A thin-section re-examination with 3 dimentional reconstruction can then be carried out on any identified pulmonary nodules, allowing further characterisation and a sensitive demonstration of nodule growth on sequential scans. The ELCAP study based in New York and Montreal examined a high-risk population of smokers and ex-smokers of over sixty years of age. Twenty seven cancers were detected in 1,000 volunteers. Of these, 26 were resectable, 23 at Stage I. All but 4 were missed on chest radiographs performed at the same attendance. Repeat screening of 623 of the volunteers after one year detected 7 further cancers of which 6 were Stage I all surgically resectable. There are no conclusive data that screening in this way will reduce the mortality from lung cancer in the population but there seems little doubt that it could do so in the light of current knowledge about the natural history and survival of treated and untreated Stage I disease.

## FLUORESCENCE BRONCHOSCOPY

Fluorescence bronchoscopy uses the principal of auto-fluorescence to detect early neoplastic and pre-neoplastic change in the bronchial mucosa. Studies by Lam and others have suggested an up to 6-fold increase in sensitivity for the detection of intra-epithelial neoplasia with little loss of specificity, these studies also demonstrating significant dysplastic and carcinoma-in-situ lesions in areas remote from the site of clinical primary disease. Other workers, notably Kurie et al have suggested that the technique is of limited value, a possible explanation being a different study group and different methodology. Our own experience suggests that the technique is useful in identifying early lesions and as a staging tool in delineating extent of disease. We have studied the technique in a heterogenous group of high-risk patients and have shown a nearly 3-fold increase in sensitivity of LIFE in comparison with white light bronchoscopy for the detection of moderate/severe dysplasia and carcinom-in-situ. A high incidence of metaplasia and dysplasia was demonstrated in the group as a whole; nearly half the biopsies were abnormal, supporting the concept of "field cancerisation" in this group. The increase in sensitivity for the detection of dysplasia is in broad agreement with Lam's initial study but has no immediate implications for treatment in the absence of knowledge of the natural history of dysplasia. There is also controversy regarding the natural history of carcinoma-in-situ but we believe that such lesions should be treated, having seen at least two such patients progress to invasive carcinoma within a few months. The detection of early intra-epithelial neoplasia, either in-situ or early invasive, offers the potential for cure with a repeatable treatment modality such as brachytherapy or photodynamic therapy which does not result in major loss of lung tissue. PDT may be particularly suitable, as a potentially repeatable therapy with no known cumulative tissue tolerance. These considerations are important in a group of patients with a substantial cumulative incidence of metachronous primary cancer, suggesting a need for careful surveillance and also the possibility of chemo-prevention.

**In summary,** lung cancer, a preventable, predictable and treatable condition, deserves a pro-active approach, using and developing epidemiological and biological methods to identify patients and populations at high risk, who can then be investigated with newer and more sensitive diagnostic techniques. The primary aim should be to "Detect, Resect" but also to consider potentially repeatable and tissue- sparing methods for the eradication of early lesions. Continued efforts regarding smoking prevention and cessation remain essential in reducing the incidence of this common and lethal condition.