Primary lung cancer is the most common cause of cancer-related death, causing 3 million deaths per year worldwide (World Health Organization [WHO] figures). Current incidence rates vary between 40 and 100 per 100,000 in Europe and 83 per 100,000 in the US. The majority (90%) of lung cancer patients die from the disease. Survival at five years remains poor – 14% at best – and only a slight improvement has been made during the past 50 years (mainly to improved surgical techniques). Surgical resection offers the only potential for cure, but is effective for only localised disease. However, localised disease is unlikely to be associated with cancer-related symptoms, so the majority of patients presenting with symptoms will be incurable. Hence, there is a strong correlation between five-year survival and stage of lung cancer: 60–80% for stage I, 30–40% for stage II, 20% for stage IIIA and <10% for stage IIIB and IV. Better survival rates have been shown for non-invasive (stage 0) lung cancer: >95% using photodynamic therapy. It is important to note that the variation in survival at different stages is not purely a selection effect, but is primarily due to the effect of treatment. Thus, in at least one controlled study, patients with stage I disease receiving treatment were found to have higher survival rates than those refusing treatment: 70 and 10% five-year survival, respectively.

It would seem logical that lung cancer must be diagnosed before symptoms occur. Such early detection requires an adequate period of time from the start of the disease process to the stage at which it can be detected by the appropriate sensitive and specific tests but before it manifests clinically with symptoms. Early detection methodologies can be applied in clinical settings such as screening and case-finding. Screening is offered to apparently healthy but at-risk individuals. In case-finding, a patient seeks advice for concerns and/or symptoms that may be related to the specific disorder. In either case, the management plan needs to be individually negotiated and discussion should include the risks as well as the benefits of testing.

The Past
A number of studies have attempted to address the question of the usefulness of screening for/early detection of lung cancer. To date, four randomised controlled studies have been undertaken using the methods of chest X-ray and routine sputum cytology. These are the Memorial Sloan Kettering Lung Project in 1984 (A), the Johns Hopkins Lung Project in 1984 (B) and the Mayo Lung Project in 1984 (C) and the Czechoslovakian Study in 1986 (D).

Studies A and B compared annual chest X-rays plus routine sputum cytology versus annual chest X-rays alone every four months for a period of five years, with follow-up for another five years. Study C compared chest X-rays plus routine sputum cytology with no routine tests every four months, again for five years with follow-up for five years. However, in this study compliance in the control (no test) group was poor in that over half had annual chest X-rays. Thus, the main question as to whether screening of any kind was better than no screening remained unanswered. In study D, the screened population underwent biannual chest X-rays plus routine sputum cytology versus no routine tests for three years, then both groups underwent annual chest X-rays plus routine sputum cytology for a further three years, with 90% compliance. All four studies confirmed that routine sputum cytology added little to chest X-ray examination in this context. It is to be noted that women were excluded from all of these trials. The main lasting conclusion from these studies was that there was no significant difference in mortality between the ‘screened’ and the control groups. This result led to the recommendation that screening using these methods is not effective and so should form a part of regular medical care in asymptomatic individuals.
“screening for lung cancer... is not recommended, either in a large-scale programme or in an individual physician’s office” and that “people with signs or symptoms should consult their physician”. Evidently, such advice is too late for the majority of lung cancer patients. An important side effect of such a nihilistic approach has been the overlooking of important technological advances over the past 20 years, which have not been applied to any significant extent. In the UK over the past 10 years, attention and funding have focused on patients presenting with symptoms accessing diagnostic and therapeutic health services as quickly as possible, i.e. presentation to treatment within six to eight weeks. As may be expected, these measures might improve palliative care but will do little to improve survival. The only way in which there is likely to be any improvement in survival will be the application of new sensitive and specific technology in high-risk individuals before they develop symptoms. The first step in the early detection of pre-symptomatic lung cancer is to identify individuals at a high risk. In order to optimise benefit/risk ratios with respect to the methodologies employed, as well as their cost-effectiveness, an attempt should be made to quantify the risk of developing lung cancer in the individual. However, individuals with significant co-morbid disease that would preclude invasive investigation and radical therapy should be excluded from a case-finding exercise. Co-morbid conditions would include severe obstructive pulmonary disease/chronic respiratory failure, severe cardiac disease and cerebral disease, subject to individual assessment.

The Future
The early detection of lung cancer begins with an assessment of the main risk factors in the study population.

Tobacco
Relative risk increases with the intensity of smoking, up to 20 times for 40 cigarettes per day compared with non-smokers. Even though quitting smoking reduces the risk, ex-smokers remain at a high risk. Currently, in North America more than half of all new lung cancer patients are ex-smokers. Passive smoking is also known to increase the risk by 1.1 in men and by 1.2 in women. The smoking risk is considerably greater for women than for men. Several studies report that women who have smoked one pack per day for 40 years are 27 times more likely to develop lung cancer than non-smokers. In men with the same smoking intensity, the risk increase was 9.6 times: almost one-third of which were lung cancers.

Pre-existing Lung Disease
This includes chronic airway obstruction and bullous lung disease. Moderate to severe chronic obstructive pulmonary disease confers a risk of developing lung cancer of between 1.4 and 4.4 times the average.

Family History
There is some evidence for a genetic predisposition to lung cancer that is expressed in smokers.

Occupational/Environmental Exposure
Environmental agents such as asbestos, radon, alkylating compounds, nickel, chromates, halo ethers and polyhydrocarbons account for between 13 and 27% of lung cancers. Thus, asbestos exposure is associated with a seven times higher risk, independent of smoking.

Previous Lung Cancer
For stage I disease, there is a local and/or systemic recurrence rate of over 25% within five years of resection, indicating a rate of approximately 5% per annum. In addition, second primary cancers developed in 34%, about one-third of which were lung cancers.

Advances in the Early Detection of Lung Cancer

Low-dose Computed Tomography Screening
The past 30 years have seen significant advances in radiological imaging, particularly computed tomography (CT). More recent developments include low-dose CT techniques that minimise radiation dose (comparable to mammography) without affecting sensitivity. Several non-randomised trials have addressed the question of the application of low-dose CT screening for lung cancer in individuals who are at risk. These studies found a lung cancer prevalence of between 1.3 and 2.8%, four times that found by chest radiographs. Furthermore, the majority of these tumours were stage I and so were amenable to curative intervention. However, several problems have been identified with these studies. These include:

- overdiagnosis bias – the diagnosis of incidental indolent tumours that may not cause the death of individual patient;
- lead time bias – the diagnosis of the disease earlier in its course, thereby giving the impression of longer survival even though the early detection and treatment have in fact not altered the progress of the disease;
- the detection of incidental benign small nodules or ‘ditzels’ that require evaluation and often repeat scans, leading to unnecessary stress and sometimes unnecessary surgical intervention;
- most of these studies were undertaken in the US and Japan, where adenocarcinoma is the most common cell type and usually a peripheral tumour. Such lesions are easily confused with benign non-calcified nodules, leading to risky invasive investigations;
- in Europe, squamous carcinoma is the most common cell type, usually arising in the central airways, and is less likely to be identified by screening; and
- more aggressive types (i.e. small-cell lung cancer) for which there is no effective cure and which have no recognised pre-malignant stage are more likely to present with symptoms as interval cancers, and therefore are less amenable to being identified by screening.
Lung Cancer

In particular, the high pick-up rate of benign lesions requiring follow-up CTs and invasive diagnostic procedures has indicated the need for better, additional screening tests that can help identify patients at a particularly high risk who will benefit from more intensive investigation and follow-up.

Quantitative Sputum Cytology – The LungSign™ Sputum Test

Sputum as a tool for early lung cancer detection and screening has a number of advantages. It is non-invasive, site-specific and inexpensive to collect. Collection can be community-based, causing minimum disruption to patients. Recent studies using automated cytometry of cells exfoliated in sputum have demonstrated an inexpensive test capable of identifying patients at a very high risk of lung cancer. This test is known as the LungSign™ test. The test is a fully automated computerised analysis of chromatin density and distribution patterns in the nuclei of respiratory epithelial cells. The test quantifies both ploidy and malignancy-associated changes (MAC), both of which are linked to lung cancer risk. Aneuploid cells have an abnormal chromosomal complement, which has been recognised as a feature of malignancy for over 50 years. The presence of these cells strongly predicts the presence of lung cancer. The MAC phenomena has also been recognised for many years, and refers to subtle changes in nuclear chromatin patterns that are seen in normal nuclei from patients harbouring a cancer. These changes are poorly understood, but have been recognised for over 50 years and have been demonstrated in a number of different cancer types. Until now, this phenomena has not been widely accepted because of poor reproducibility. The use of computerised image analysis enables accurate quantification of this phenomenon so that it can be harnessed for routine practice. They have been detected in a number of different cancer types, and cell culture studies have recapitulated these changes in vitro.

In the published trial this test demonstrated an ability to detect lung cancer with a sensitivity of 40% and a specificity of 90%. Assuming a cut-off sputum cytometry score giving 91% specificity had been selected as an indication to investigate for cancer in this trial, a total of 191 patients would have been positive, of whom 132 did indeed have cancer, leaving 59 false-positives. Translating these results to a screening population of asymptomatic smokers with chronic obstructive pulmonary disease and assuming a prevalence rate for cancer of around 3%, for every 1,000 patients screened a specificity of 91% would detect 12 of the 30 cancers expected at the expense of investigating seven false-positives for each detected cancer. However, these assumptions are based on a single sputum test. Unknown at this stage is the performance of the test in a serial testing application – do score changes between repeated tests hold any significance? Besides screening, there are other uses for this novel test also worth of further research, namely whether the test could be used to stratify CT-detected nodules into low- and high-risk groups, and whether it may be a non-invasive way to follow up patients previously treated for lung cancer.
Now there’s a NEW test that helps detect Early-Stage lung cancer using advanced image cytometry.

Introducing LungSign™

LungSign™ is a DNA cytometry sputum test that brings added insight to early lung cancer detection.

To order a LungSign™ test or get more details, call 011-604-629-8785 (Canada) or visit: www.lungsign.com.

CT scans only tell part of the story.

LungSign™ is a trademark of Perceptronix Medical, Inc.
©Copyright 2007 Perceptronix Medical, Inc. November 2007