Advances in Diagnosis of Early Lung Cancer

a report by
D Paul Dhillon *and* **David RJ Snead**

University Hospitals Coventry and Warwickshire NHS Trust

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.[1] Since 1960, the rate of rise in lung cancer deaths in women has been especially high, whereas death rates in men have plateaued. Death rates in Scottish women are the highest in the world, at 28 per 100,000.[1] The majority (90%) of lung cancer patients die from the disease.[2] 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).[1] 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,[3] 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.[4–8] Better survival rates have been shown for non-invasive (stage 0) lung cancer: >95% using photodynamic therapy.[9] 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.[10,11]

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.[12]

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),[13,14] the Johns Hopkins Lung Project in 1984 (B),[15,16] the Mayo Lung Project in 1984 (C)[17] and the Czechoslovakian Study in 1986 (D).[18,19]

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 tests) 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.[20]

There is general acceptance that disease-specific mortality is the best measure of effectiveness of early-detection programmes. Other variables, such as length of survival after diagnosis, are deemed to be subject to biases such as overdiagnosis, lead time and length time. That this may not necessarily be the case for lung cancer is eloquently argued by Strauss et al.[21] A recent re-analysis of the data from the Mayo Lung Project suggests a different conclusion. When the fatality ratio (number of lung cancer deaths/total number of lung cancers) was used instead of the mortality rate (number of lung cancer deaths/total number of subjects studied) to compare the screened with the control populations, a significant survival benefit from screening with chest X-ray was observed.[22] Thus, even plain chest X-ray may provide a five-year survival benefit, but routine sputum cytology appears to be unhelpful. As these major trials were published over 20 years ago, a number of influential societies (including the American Society of Radiology and the American College of Radiology [ACR]) have concluded that

D Paul Dhillon is a Consultant Chest Physician at University Hospitals Coventry and Warwickshire NHS Trust. He qualified in medicine at Cambridge University and St George's Medical School, London in 1975, and completed his training in respiratory medicine at the Brompton Hospital, London.

E: paul.dhillon@uhcw.nhs.uk

David RJ Snead is a Consultant Pathologist at University Hospitals Coventry and Warwickshire NHS Trust. He was appointed Consultant in Coventry in 1997 and his main interests include the tumour biology and early diagnosis of lung cancer. Dr Snead trained in histopathology at Queens Medical Centre, Nottingham and Frenchay Hospital, Bristol, and qualified in medicine from St Thomas' Hospital Medical School, University of London in 1989.

E: david.snead@uhcw.nhs.uk

"screening for lung cancer… is not recommended, either in a large-scale programme or in an individual physician's office"[23] and that "people with signs or symptoms should consult their physician".[24] 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/or radical therapy should be excluded from a case-finding exercise. Co-morbid conditions would include severe obstructive pulmonary disease/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.[25] Even though quitting smoking reduces the risk, ex-smokers remain at a high risk.[4] Currently, in North America more than half of all new lung cancer patients are ex-smokers.[5] Passive smoking is also known to increase the risk by 1.1 in men and by 1.2 in women.[26] 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.[27,28] In men with the same smoking intensity, the risk increase was 9.6 times: almost one-third the risk of smoking in women. Furthermore, 40% of lung cancers in women are diagnosed before 60 years of age.[29,30]

Age

Incidence of lung cancer increases rapidly for those who are between 40 and 80 years of age.[31,32]

Pre-existing Lung Disease

This includes chronic airway obstruction[33] and bullous lung disease.[34] Moderate to severe chronic obstructive pulmonary disease confers a risk of developing lung cancer of between 1.4 and 4.4 times the average.[35]
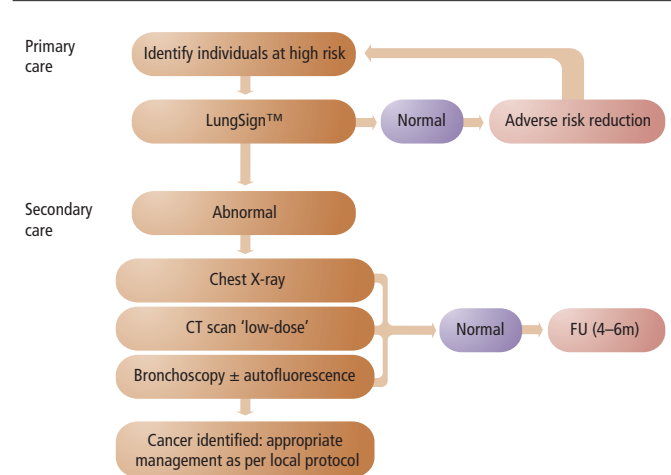
Family History

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

Figure 1: Investigation Pathway for Early Diagnosis of Lung Cancer

between 13 and 27% of lung cancers.[36] 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.[7] 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.[37,38] 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.[39–43] 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 1A 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.

In particular, the high pick-up rate of benign lesions requiring follow-up CTs and invasive diagnostic procedures[44,45] has indicated the need for better, additional screening tests that can help identify the 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 chromosome complement, which has been a recognised feature of malignancy for over 50 years.[46] 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.[47] 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[48] 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.[49,50]

In the published trial this test demonstrated an ability to detect lung cancer with a sensitivity of 40% and a specificity of 90%.[51] 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 worthy 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. ■

1. Wingo WA, Tong T, Bolden S, Cancer Statistics, *CA C J Cancer Clin*, 1995;45:8–30.
2. Melamed MR, Flehinger BJ, Early lung cancer as a potential target for chemoprevention, *J Cell Biochem*, 1993;17F:57–65.
3. Carbone PP, Frost JK, Feinstein AR, et al., Lung Cancer: Respectives and Prospects, *Ann Int Med*, 1970;73:1003–24.
4. Halpern M, Gillespie B, Warner K, Patterns of absolute risk of lung cancer mortality in former smokers, *J NCI*, 1993;85:457–64.
5. Tong L, Spitz MR, Fueger JJ, et al., Lung carcinoma in former smokers, *Cancer*, 1996;78:1004.
6. Brown CC, Kessler LG, Projections of lung cancer mortality in the US, *J Nat Canc Inst*, 1988;80:43–51.
7. Martini N, Bains MS, Burt ME, et al., Incidence of local recurrence and second primary tumours in resected stage I cancer, *J Thorac Cardiovasc Surg*, 1995;109:120–29.
8. Canadian Cancer Statistics, National Cancer Institute, 1996.
9. Lam S, Photodynamic Therapy of Lung Cancer, *Sem Oncol*, 1994;21:615–19.
10. Flehinger BJ, Kimmel M, Melamed M, The effect of surgical treatment on survival from early lung cancer, *Chest*, 1992;101:1013–18.
11. Sobue T, Suzuki T, Naruke T, et al., The Japanese Lung Cancer Screening Research Group. A case-control study for evaluating lung cancer screening in Japan, *Int J Cancer*, 1992;50:230.
12. Wolpaw DR, Early Detection in Lung Cancer. Case finding and screening, *Med Clin North America*, 1996;80(1):63–82.
13. Melamed MR, Flehinger BJ, Zaman MB, et al., Screening for Early Lung Cancer: Results of the Memorial Sloan-Kettering Study, *Chest*, 1984;86:44–53.
14. Flehinger BJ, Melamed MR, Zaman MB, et al., Early Lung Cancer Detection: Results of the initial (prevalence) radiological and cytologic screening the Memorial Sloan-Kettering study, *Am Rev Resp Dis*, 1984;130:555–60.
15. Tockman M, Survival and mortality from lung cancer in a screened population: The Johns Hopkins Study, *Chest*, 1986;89:325–6S.
16. Frost JK, Ball WC, Levin ML, et al., Early Lung Cancer Detection: Results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study, *Am Rev Resp Dis*, 1984;130:549–54.
17. Fontana RS, Sanderson DR, Taylor WF, et al., Early Lung Cancer Detection: Results of the initial radiological and cytological screening – The Mayo Clinic study, *Am Rev Resp Dis*, 1984;130:561–5.

18. Kubik A, Polak J, Lung Cancer Detection: Results of a randomised prospective study in Czechoslovakia, *Cancer*, 1986;57:2428–37.
19. Kubik A, Parkin DM, Khlat M, et al., Lack of benefit from semi-annual screening for cancer of the lung: Follow-up report of a randomised controlled trial on a population of high-risk males in Czechoslovakia, *Int J Cancer*, 1990;45:26–33.
20. Canadian Guide to Clinical Preventive Healthcare, 1994;780–86.
21. Strauss GM, Gleason RE, Sugarbaker DJ, Screening for lung cancer: Another look, a different view, *Chest*, 1997;111(3):754–68.
22. Strauss GM, Gleason RE, Sugarbaker DJ, Chest x-ray screening improves outcome in lung cancer: A reappraisal of randomised trials on lung cancer screening, *Chest*, 1995;107:270–79S.
23. Eddy D, Screening for lung cancer, *Ann Intern Med*, 1989;111:232–7.
24. American Cancer Society, Report on the cancer-related health checkup: lung cancer, *CA Cancer J Clin*, 1980;30199–207.
25. American Cancer Society, Cancer facts and figures, 1988.
26. American Cancer Society, Cancer facts and figures, 1994.
27. Risch HA, Howe GR, Jain M, et al., Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type, *Am J Epid*, 1993;138(5):281–93.
28. Zang EA, Wynder EL, Differences in lung cancer risk between men and women, *J NCI*, 1996;88:183–92.
29. McDuffie HH, Klaassen DJ, Dosman JA, Female–male differences in patients with primary lung cancer, *Cancer*, 1987;59:1825–30.
30. Risch HA, Howe GR, Jain M, et al., Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type, *Am J Epid*, 1994;140(2):185–6.
31. Melamed MR, Flehinger BJ, Early lung cancer as a potential target for chemoprevention, *J Cell Biochem*, 1993;17F:57–65.
32. Sondik E (ed.), *Annual Cancer Statistics Review*, Division of Cancer Prevention and Control, National Cancer Institute, 1989.
33. Tockman MS, Anthonisen NR, Wright EC, et al., Airway obstruction and the risk for lung cancer, *Ann Intern Med*, 1987;106:512–18.
34. Goldstein MJ, Snider GL, Liberson M, et al., Bronchogenic carcinoma and giant bullous disease, *Am Rev Resp Dis*, 1968;1062–70.
35. Brody JS, Spira A, State of the Art: COPD, inflammation and lung cancer, *Proc Am Thorac Soc*, 2006;3:535–8.

36. Huuskonen MS, Screening for occupational cancer, *Scand J Work Environ Health*, 1992;18(Suppl. 1):110–14.
37. Diedrich S, Wormanns D, Heindel W, Low-dose CT: a new tool for screening lung cancer?, *Eur Radiol*, 2001;11:1916–24.
38. Gartenschlager M, Schweden F, Gast K, et al., Pulmonary nodules: detection with low-dose versus conventional spiral CT, *Eur Radiol*, 1998;8:609–14.
39. Henschke C, Mcauley D, Yankelevitz D, et al., Early lung cancer detection project: overall design and findings from baseline screening, *Lancet*, 1999;354:99–105.
40. Sone S, Takashima S, Li F, et al., Mass screening for lung cancer with mobile spiral CT scan, *Lancet*, 1998;35:1242–5.
41. Sobue T, Mariyama N, Kaneko M, et al., Screening for lung cancer with low-dose helical CT, *J Clin Oncol*, 2002;20:911–20.
42. Swensen S, Sloan J, et al., Screening for lung cancer with low-dose spiral computed tomography, *Am J Respir Crit Care Med*, 2002;165:508–13.
43. MacRedmond R, Logan PM, Lee M, et al., Screening for lung cancer using low-dose CT scanning, *Thorax*, 2004;59:237–41.
44. Swensen S, Jett J, Hartman D, et al., CT screening for lung cancer: five-year prospective experience, *Radiology*, 2005;235:259–65.
45. van de Weil J, Wang D, Xu H, et al., Neglectable benefit of searching for incidental findings in Dutch-Belgian lung cancer screening trial (NELSON) using low-dose multidetector CT, *Eur Radiol*, 2007;17:1474–82.
46. Rabotti G, Ploidy of primary and metastatic human tumors, *Nature*, 1959;183:1276–7.
47. Nieburg HE, Recent progress in the interpretation of malignancy associated changes (MAC), *Acta Cytol*, 1968;12:445–53.
48. Sun X, Zheng Y, MacAulay C, et al., *In vitro* model for studying malignancy-associated changes, *Analytical Cell Pathol*, 2003;25:95–102.
49. Guillaud M, Doudkine A, Garner D, et al., Malignancy-associated changes in cervical smear: systematic changes in cytometric features with the grade of dysplasia, *Annals Cell Pathol*, 1995;9:191–204.
50. Us-Krasovec M, Erzen J, Zganec M, et al., Malignancy-associated changes in epithelial cells of buccal mucosa: a potential cancer detection test, *Annals Quant Cytol Histol*, 2005;27:254–62.
51. Kemp R, Reinders D, Turic B, Detection of lung cancer by automated sputum cytometry, *J Thorac Oncol*, 2007;2:993–1000.

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.

CT scans only tell part of the story.

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

LungSign™
Early detection, better outcomes