Population screening for lung cancer

Peter Armstrong, Janet E Husband, John A Holemans

The feasibility of diagnosing small stage I lung cancers using low-dose chest computed tomography in asymptomatic at-risk individuals has been demonstrated in multiple studies. However, it has yet to be proved that the introduction of a chest computed tomography screening programme would do more good than harm at an acceptable cost.

Screening for lung cancer using low-dose spiral computed tomography (CT) is a topic which has stimulated much discussion during recent years, but as yet no firm conclusions can be drawn regarding its potential value. The underlying concept of an early lung cancer detection programme is that more cures can be achieved when stage 1A tumours are detected in asymptomatic individuals compared with patients who first present at a later stage or with symptoms. This is because the surgical results and 5-year survival rates are significantly better in those with early disease: the average 5-year survival for all lung cancers is close to 15% (Jemal et al, 2002) whereas 5-year survival rates for stage 1A non-small cell carcinomas are 67% or even higher in some series (Mountain, 1997; Naruke et al, 2001). Non-small cell lung cancer accounts for about 70% of all lung cancers.

The use of low-dose spiral CT as a screening tool for lung cancer was pioneered by Kaneko et al (1996) and Sone et al (1998) in Japan, by Henschke and colleagues (1999) in the USA and by Diederich et al (2000) in Germany. These groups have clearly demonstrated that spiral CT can identify small peripheral lung cancers in asymptomatic individuals and their reports have been met with much enthusiasm. As a result, in a bid to determine the benefit, if any, of CT-based lung cancer screening several countries have now commenced both non-randomized and randomized trials and others, including the UK, have developed detailed proposals for trials which are as yet unfunded.

In the UK there are approximately 38 000 new cases of lung cancer diagnosed annually (Cancer Research UK, 2003). The vast majority of cases are the result of cigarette smoking and the most recent UK statistics from 2003 have revealed that lung cancer accounted for 22% of all cancer deaths in the UK (Cancer Research UK, 2003). Mortality from lung cancer has been declining over recent years, yet in men it remains the most common cause of cancer death and in women lung cancer is now the leading cause of cancer death, overtaking breast cancer mortality for the first time (Cancer Research UK, 2003).

The *NHS Cancer Plan* aims to reduce mortality from cancer by improved quality of patient care throughout the UK via earlier diagnosis and the instigation of prompt appropriate up-to-date treatment (Department of Health, 2000). While the best way to reduce lung cancer mortality is disease prevention through smoking cessation programmes, it is unlikely that reduction in smoking would be of sufficient magnitude to make a major impact on lung cancer mortality in the foreseeable future.

Lung cancer screening in high-risk groups therefore offers an attractive alternative, giving individuals in whom early lung cancers are detected the possibility of cure through early therapeutic intervention. However, the presumption that earlier diagnosis using low-dose spiral CT necessarily equates to a decrease in mortality from lung cancer is simplistic, because there are so many variable factors and inherent biases to take into account (Black, 2000a; Patz et al, 2000a; Ellis and Gleeson, 2001; Ellis et al, 2001). Such biases were clearly apparent in earlier lung cancer screening trials using chest radiography and sputum cytology.

EARLY LUNG CANCER SCREENING TRIALS

Increasing rates of lung cancer in the 1960s and 1970s led the National Cancer Institute (NCI) to sponsor three large prospective randomized controlled trials (RCT) of lung cancer screen-

Professor Peter Armstrong is Professor of Radiology, St Bartholomew's Hospital, London, **Professor Janet E Husband** is Professor of Diagnostic Radiology, Royal Marsden Hospital, Sutton, Surrey SM2 5PT and **Dr John A Holemans** is Chair Division of Radiology, The Cardiothoracic Centre – Liverpool, Liverpool

Correspondence to: Professor JE Husband

ing (Flehinger et al, 1984; Fontana et al, 1986; Tockman, 1986). A fourth large RCT was also conducted in Czechoslovakia (Kubik et al, 1990, 2000). Although other smaller non-randomized controlled studies of lung cancer screening were undertaken in the 1970s (Brett, 1968; Nash et al, 1968; Wilde, 1989), most attention has been focused on the results of the four major studies which all compared chest radiography, with or without sputum cytology, with a control group.

The multicentre survey conducted by the NCI between 1971 and 1983 has been extensively analysed and is the only one that will be discussed in this article. In total, 0.73% of individuals were diagnosed with lung cancer at their initial screening (Flehinger et al, 1984; Fontana et al, 1984, 1986; Frost et al, 1984; Heelan et al, 1984; Sanderson, 1986; Tockman, 1986). In the Mayo Lung Project section of the study, approximately 9000 men over 45 years of age who were chronic heavy cigarette smokers, but with no medical contraindications to surgery, participated. After excluding nearly 1000 individuals who were ruled ineligible because of serious medical problems, this portion of the study (Fontana et al, 1986, 1991) then randomly selected half of the subjects to undergo surveillance by chest radiography and sputum cytology every 4 months, and half to a control group who were recommended to have annual chest radiographs and sputum cytology.

The rate of cancer diagnosis in the screened group was 5.5 per 1000 per year, compared with 4.3 per 1000 per year in the control group. The resectability rate was higher in the screened group (46%) than in the control group (32%) and the median survival was at least three times better in the study group, but after a median of 20 years the lung cancer deaths were virtually identical in the two groups: 4.4 per 1000 in the screened arm compared to 3.9 per 1000 in the control group (Marcus et al, 2000). The apparent disparity between the greatly improved survival and the lack of improvement in mortality from lung cancer is believed to be a result of overdiagnosis in the screened population (Eddy, 1989; Marcus et al, 2000).

The conclusions drawn from analysis of the results were that large-scale radiographic and cytological screening for lung cancer did not result in a mortality benefit. Critics of this conclusion have argued that there might have been a benefit to a subset of patients and that the chest radiography component of the study only had the power to show a reduction in mortality of 50%, rather than a more realistic expectation of between 10 and 20% (Eddy, 1989; Rubin, 1991; Henschke and Yankelevitz, 2000; Miettinen, 2000). However, a subsequent detailed re-analysis of the data has confirmed the initial conclusions (Marcus et al, 2000; Manser et al, 2003).

The Prostate, Lung, Colon and Ovarian study is a randomized controlled trial (RCT) which is currently underway and is funded by the NCI. This trial aims to determine the role of annual chest radiography in screening for lung cancer. The study has been designed with a power of 89% to detect a difference in lung cancer mortality of 10% (Gohagan et al, 1995). While the results of this study are expected in the not too distant future, the introduction of low-dose spiral CT may have superseded the potential value of chest radiography as a method of lung cancer screening.

IMPORTANT BIASES IN CANCER SCREENING PROGRAMMES

Three fundamental biases need to be considered in relation to interpretation of lung cancer screening trials: lead-time bias, length bias and overdiagnosis bias.

Lead-time bias

The term 'lead-time bias' refers to the extra life expectancy that occurs simply from diagnosing a tumour earlier, regardless of whether or not treatment is effective. In other words, moving the time of diagnosis of a lung cancer forward inevitably improves 5-year survival rates, which are calculated from the time of diagnosis, regardless of the effect on mortality.

Length bias

'Length bias' refers to the tendency for tumours with an inherently better prognosis to be discovered by population screening because they are slower growing lesions. This is particularly important on the first round (referred to in screening parlance as the 'prevalence' round) of screening because fast-growing tumours present with symptoms more rapidly and these patients are unlikely to present themselves for screening.

Overdiagnosis bias

'Overdiagnosis bias' is similar to length bias; it refers to overdiagnosing a benign lesion as a malignant tumour, or diagnosing a very slow growing malignancy that would not cause clinical disease or death of the patient during his or her natural life expectancy (Black, 2000a).

Atypical adenomatous hyperplasia (originally referred to as bronchioloalveolar cell adenoma), is a relatively recently described pathological process which may be of particular relevance. It is for practical purposes only recognized in vivo on chest CT (Miller, 1990; Vazquez and Flieder, 2000; Kawakami et al, 2001). Histopathologists vary considerably among themselves over whether they designate very small lung lesions as atypical adenomatous hyperplasia (believed to be either a benign process or a preinvasive carcinoma), or whether they classify the lesion in question as invasive carcinoma.

These biases can be minimized by comparing disease-specific deaths (that is, deaths resulting from lung cancer) in a RCT of a screened *vs* a non-screened population with sufficiently long follow up to compensate for lead-time bias. A fourth potential bias operates even in RCTs, namely selection bias, where conclusions may be based on series of patients in whom the randomization procedure does not produce groups which are representative of the population at large. Patients who self select for screening trials tend to be well informed and motivated to undergo regular follow up, whereas in population screening programmes the screened population tends to be more heterogeneous.

In general screening programmes diagnose disease early, but those that do not lead to reduced mortality from the disease being detected have the following characteristics when compared to historical or non-random controls:

1. Earlier stage at diagnosis and consequently improved resectability rates
2. Improved survival
3. Higher proportion of cancers
4. No change in the number of late stage tumours
5. No reduction in mortality.

Survival following surgical resection from lung cancer is complex and multifactorial, and depends not only on tumour size and stage, but also on the ability of the tumour to metastasize and the ability of the body defence systems to destroy micrometastases. Many other poorly understood host and tumour factors are also involved in determining the balance between tumour growth and destruction (Black, 2000b; Patz et al, 2000b).

LUNG CANCER SCREENING USING LOW-DOSE SPIRAL CT

Low-dose spiral CT has now been used for almost a decade as the primary technique for screening populations at risk for lung cancer. All the programmes have used low-dose CT (40 and 50 mA and between 120 and 140 kVp).

The results from the major published studies are listed in *Table 1*. For comparison the results from screening programmes for breast cancer with mammography show a yield of 0.7% at initial screening.

There are several important conclusions which can be drawn from these early lung cancer screening programmes:

- The diagnostic yield of lung cancer from CT is far superior to that of chest radiography. At least twice as many small lung cancers are visible on CT than on plain chest radiography. The lesions that are invisible on chest radiographs are either below the size threshold for non-calcified nodule detection, are obscured by overlying structures or are shown to have infiltrating and, therefore, relatively ill-defined margins (Yang et al, 2001a).

TABLE 1.
Low-dose computed tomography screening results

	USA*	Japan†	Japan‡	Germany§	USA¶
Number of individuals	1000	1369	5483	817	1520
Age (years)	>60	>50	>40	>40	>50
Number of patients with lung cancer in prevalence round	27	3/663	22	11	26
% of patients with lung cancer in prevalence round	2.7	0.4	0.40	1.3	1.5
Number of patients with lung cancer in incidence round(s)	7	7/706 in 1st twice yearly screen, 5/1111 in second or later twice yearly screen	25/4425 in 1st annual screen, 9/3878 2nd annual screen	Not available	10 in two incidence rounds
% of patients with lung cancer in incidence round(s)	0.59	1.0 in first rescreen, 0.2 in subsequent screens	0.56 in 1st annual screen, 0.23 in 2nd annual screen	Not available	0.20
Stage 1 (%)	85	93	88	73	60

*Henschke et al (1999, 2001); † Kaneko et al (1996, 2000); ‡ Sone et al (2001); § Diederich et al (2002); ¶ Swensen et al (2002, 2003).

- A very high proportion of the cancers diagnosed are stage 1 (57–85%) and most of these are stage 1A. One of the primary objectives of screening is therefore fulfilled, namely to diagnose asymptomatic early stage disease.
- The cancer diagnosis rate is highly dependent on inclusion criteria. A greater incidence of lung cancer is found when the age of those screened is above 60 years, and when the screening CT is limited to those with a heavy smoking history.
- The detection rate of benign nodules is very high. Up to 98% of non-calcified nodules detected in the USA trials reported to date were benign. While this in part may be a result of the high incidence of histoplasmosis in the USA, the incidence of benign nodules is also very high in Europe (Diederich et al, 2002), where histoplasmosis is rare.
- As anticipated in all screening programmes, both the detection rate of lung cancers and the false positive rate are reduced considerably on annual follow-up screening (incident screen). However, the false positive rate may still be as high as 14% (Swensen et al, 2003).

APPEARANCE OF LUNG CANCERS DETECTED IN SCREENING PROGRAMMES

Cancers detected by CT screening may be:

- Pure ground-glass density (*Figure 1*)
- A central solid nodule (i.e. soft tissue density) surrounded by ground-glass shadowing (*Figure 2*)
- Homogeneously solid (i.e. wholly soft tissue density) (*Figure 3*)
- Heterogeneous low density and soft tissue density.

During recent years an enormous amount of data on the appearances of screen-detected lung cancers has been accrued (Aoki et al, 2000; Yang et al, 2001b; Henschke et al, 2002). The less solid the component, the less visible the lesion is at plain chest radiography (Yang et al, 2001b). Also the greater the proportion of ground-glass shadowing the more likely it is that the lesion will grow relatively slowly (Aoki et al, 2000; Henschke et al, 2002) and will be a well-differentiated tumour, such as a bronchioloalveolar carcinoma or atypical adenomatous hyperplasia (Yang et al, 1999; Kodama et al, 2002; Suzuki et al, 2002). Nodules that grow quickly tend mostly to be either homogeneously or predominantly solid at CT (Wang et al, 2000).

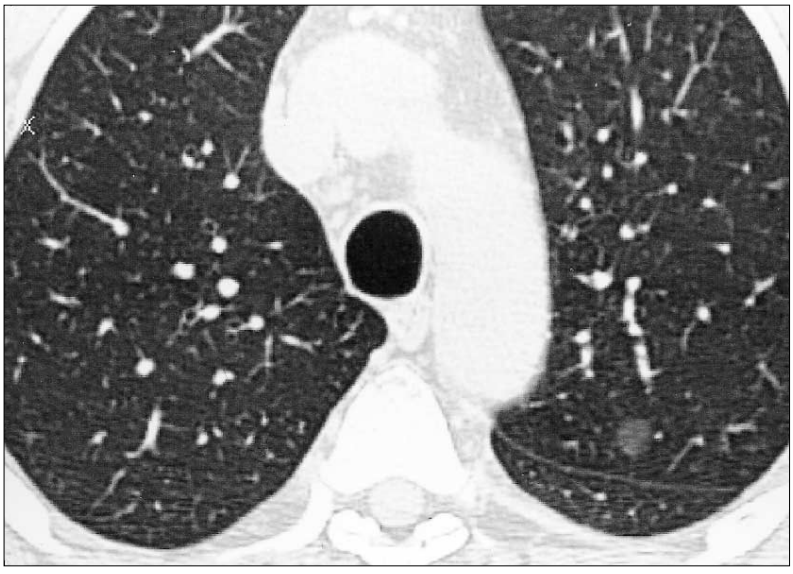

Figure 1. 8 mm pure ground-glass opacity pulmonary nodule in left upper lobe. This nodule was followed up for 2 years and remained stable. 18F-fluorodeoxyglucose positron emission tomography was negative. The patient declined resection of the lesion.

IMAGING ALGORITHMS TO DETERMINE THE NATURE OF A SMALL PULMONARY NODULE

Screening studies using low-dose spiral CT have revealed that a large number of indeterminate non-calcified pulmonary nodules are detected of which only a small proportion prove to be malignant. These non-calcified nodules range in size from only a few millimetres to over a centimetre in diameter. Nodules less than 1 cm in diameter are usually impossible to characterize on CT and are not in general suitable for biopsy, positron emission tomography (PET) or contrast enhancement. Indiscriminate surgical resection of these small nodules, most of which would prove to be benign, would severely disadvantage a large number of individuals.

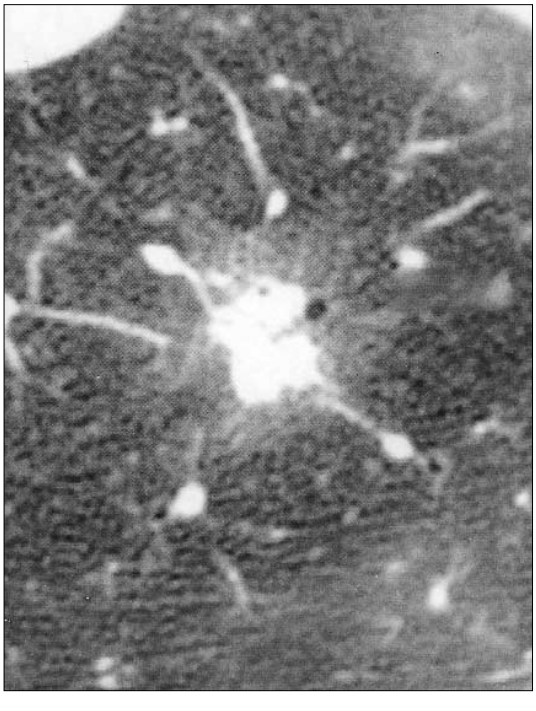

Figure 2. 12 mm part solid pulmonary nodule with a central solid core surrounded by ground-glass opacity.

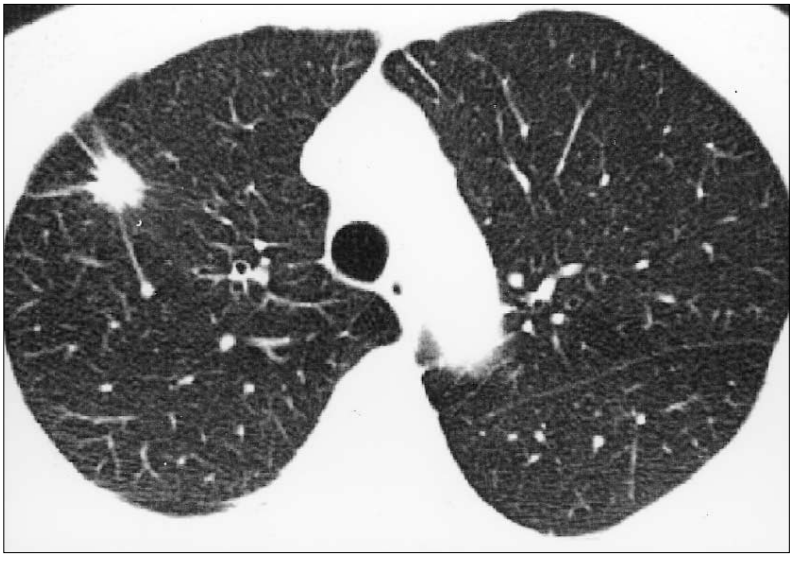

Figure 3. 14 mm spiculated solid pulmonary nodule right upper lobe.

A strategy for evaluating non-calcified nodules detected on screening is therefore required. The basic principles underlying the diagnostic approach to individual nodules detected during a lung cancer CT screening programme are similar to those described for a solitary pulmonary nodule first detected on plain chest radiography. There is, however, one very important difference. It is generally regarded as unwise to leave a nodule larger than 1 cm with imaging characteristics compatible with bronchial carcinoma for annual follow up because the delay inherent in this would be detrimental to life expectancy. Follow up alone to observe nodule growth is an accepted approach for nodules under 1 cm in diameter, largely because of the much higher probability of any particular nodule being an incidental benign lesion.

The hope is that the benefit of some delay, to check that the growth rate is compatible with lung cancer, thereby avoiding unnecessary surgery, will outweigh the disadvantage of delaying treatment for what should still be a small tumour at the time of surgery. However, it is important to note that benign tumours may grow and in the series reported by Swensen et al (2003) from the Mayo Clinic, five out of eight benign lesions showed growth on follow up and eight patients underwent thoracotomy for benign lesions; in total, 21% of surgical resections were deemed unnecessary.

A variety of algorithms, which differ in points of detail, have been recommended (Yankelevitz and Henschke, 2000; Aberle et al, 2001; Diederich et al, 2002; Swensen et al, 2002). One approach, advocated by the authors of this article, is:

- To recommend follow up at 12 months for individuals with one to six nodules, none of which exceeds 4 mm in diameter. The concept behind this recommendation is that, based on the growth rate expected for 90% of non-small cell lung cancers, any nodule that is in fact a small bronchial carcinoma will still be no bigger than 10 or 11 mm in diameter at an annual follow up.
- Individuals with more than six nodules, all of which are under 1 cm in diameter, can be assumed to have multiple granulomas and should undergo annual screening in the same manner as subjects who have a normal chest CT.
- A cluster of nodules (i.e. two or more nodules, none of which is more than 1 cm distant from an adjacent nodule), all of which are less than 1 cm in diameter, should be regarded as being caused by tuberculosis or histoplasmosis; there is a very low probability of any individual nodule being lung carcinoma.
- The shape and density of nodules between 5 and 10 mm in diameter should be assessed. If the lesion is clearly linear, or Y-shaped, or shows other specifically benign features such as fat or a benign pattern of calcification, the lesion can be assumed to be benign.
- If none of these specific benign features are present, then follow-up CT after 3 months should be performed to determine lesion growth. The frequency of follow up beyond 3 months should be tailored to the estimated range of possible growth rates determined at the first 3-month review. Growth rates are expressed as the time taken for the nodule to double in volume.
- The total follow-up period should be 2 years. A nodule that shows a volume doubling time compatible with lung cancer, namely between 1 month and 18 months, should be assumed to be a carcinoma and treated appropriately. However, there are important caveats; a nodule that shows no growth over a 2-year period is very unlikely to be malignant, but it is important to emphasize that 2-year stability does not totally rule out lung carcinoma (Yankelevitz and Henschke, 1997); very slow growth of adenocarcinomas with doubling times of up to 48 months have been reported (Hasegawa et al, 2000) and slow growth does not exclude bronchial carcinoid.
- For those centres with ready access to PET, it is reasonable to perform PET on nodules above 5 mm in diameter and expedite biopsy for a nodule which shows abnormal uptake of

the tracer (Marom et al, 2002). It is important to recognize, however, that a negative PET for nodules less than 1 cm is unreliable evidence of benignity (Pastorino et al, 2003).

- Above 1 cm in diameter, the approach is identical to that described for a solitary pulmonary nodule discovered on plain chest radiography.

It is important not to underestimate the difficulty of accurately determining the growth rate of nodules under 1 cm in diameter. A nodule has to increase its diameter by only 26% to double its volume. For example, a 5 mm nodule which doubles in volume during a 6-month period will increase in diameter by just 1.25 mm, a difference which requires meticulous methods of nodule measurement, preferably using dedicated computer software which is now becoming more widely available (Zhao et al, 1999) (*Figure 4*). With appropriate software it is possible to achieve accuracies for volume measurement with phantom nodules of within 3%, but interobserver agreement can differ in vivo by up to 20% (Wormanns et al, 2000). Three-dimensional computerized techniques demonstrate asymmetrical growth better than two-dimensional displays. Asymmetrical growth is diagnostically useful because it is frequently observed in cancerous nodules (Yankelevitz et al, 1999). To gain widespread application, however, the various computerized methods will need to be integrated into clinical practice more widely and will need to be quick and easy to apply.

Advances in technology, notably multidetector CT scanners, cine viewing, computerized nodule detection systems and three-dimensional reconstruction techniques (Tillich et al, 1997; Armato et al, 1999, 2001, 2002; MacMahon et al, 1999; Reeves and Kostis, 2000; Ko and Betke, 2001; Wormanns et al, 2002) may improve the ability of low-dose helical CT to detect and accurately characterize lung nodules, but all the available systems both under- and overdiagnose nodules compared to human observers and therefore are likely to be used as adjuncts, or as a 'second reader' alongside radiologists' own interpretation.

THE NEED FOR A RANDOMIZED CONTROLLED TRIAL

The central aim of any population screening programme is to do more good than harm at a cost which is acceptable to society. The potential beneficial effects of a lung cancer CT screening programme are that it might extend life by reducing mortality resulting from the lung cancer. Potential harmful effects include extra radiation from repetitive CT examinations and the consequences of false positive diagnoses, notably anxiety as a result of the lead time, anxiety and complications from unnecessary further imaging, biopsy and even surgery.

There has been considerable debate regarding the advisability of introducing large-scale low-dose spiral CT screening for the early diagnosis of lung cancer (Smith, 1999; Miettinen, 2000; Henschke and Yankelevitz, 2000; Patz et al, 2000a, 2001; Aberle et al, 2001; Miettinen and Henschke, 2001; Heffner and Silvestri, 2002). The debate centres on the significance of the various biases outlined at the beginning of this article in the face of the clearly demonstrated ability of CT to detect lung cancers under 1 cm in size at a time when the tumour is still stage 1A. It will take a RCT with many years of follow up to determine any mortality reduction and until this vital piece of information is known it will not be possible to calculate the cost in any meaningful way. The standard way of considering financial cost is to calculate the monetary cost per quality adjusted life year (QALY) saved. One study by Mahadevia et al (2003) has shown disappointing results but it will require a full analysis of the long-term results of RCTs to fully answer the questions related to costs and benefits of population screening with certainty.

Therefore the fundamental questions to be answered in the large-scale randomized trials currently being conducted by the NCI in the USA and other studies being carried out in Europe are as follows:

1. Does early detection using up-to-date multidetector spiral CT result in a measurable reduction in the mortality of lung cancer?
2. Can thoracotomy be limited largely to those patients with life-threatening malignancies?
3. Can mass screening with helical CT be performed in a cost-effective manner?

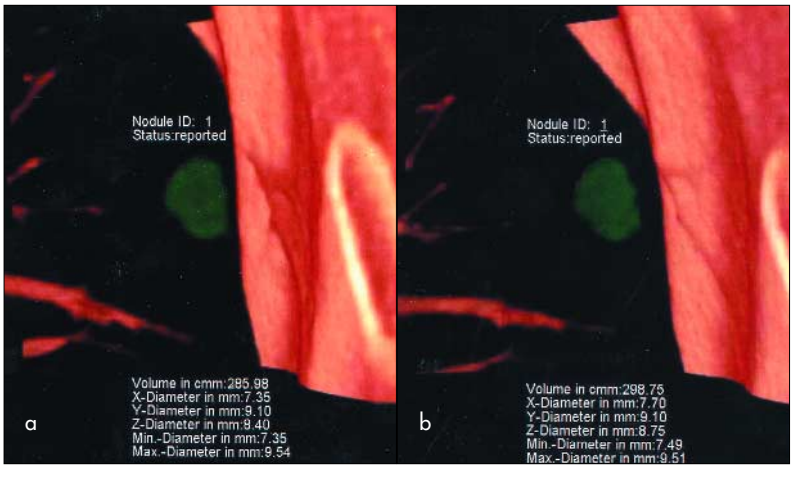

Figure 4. Pulmonary nodule analysed using syngo Lung Care software (Siemens AG, Erlangen, Germany). a. 286 mm^3 nodule at baseline and (b) 13 mm^3 interval growth to 299 mm^3.

CONCLUSIONS

There is no evidence that population screening using chest radiographs saves lives in patients with lung cancer. There has been considerable debate and controversy regarding the advisability of introducing large-scale low-dose spiral CT screening for the early diagnosis of lung cancer. The debate centres on how important the various biases are in the face of the clearly demonstrated ability of CT to detect lung cancers under 1 cm in diameter at a time when the tumour is still at an early stage and is deemed resectable. We will need to await the outcome of large randomized trials to answer these tantalizing questions. In the UK lung cancer remains the leading cause of cancer death in both males and females and new approaches to lung cancer detection and treatment must be pursued if we are to make any headway in combating this disease.

Smoking prevention is clearly an important component of any fight against lung cancer but other measures including the investigation of biomarkers for early detection and chemoprevention therapies are also important initiatives (Mulshine and Hirsch, 2003). Low-dose spiral CT for detection of lung cancer in asymptomatic individuals is already creeping into clinical practice in the UK but the relative incidence of lung cancer in high-risk asymptomatic individuals and of benign nodules in the UK population is unknown. Therefore in the authors' view there remains a place for a pilot study of lung cancer screening in the UK to determine the practicalities, benefits and disadvantages of a full-scale lung cancer spiral CT screening programme in this country. HM

Figure 4 *is reproduced by kind permission of Siemens Medical Solutions.*

Conflict of interest: PA has acted as a consultant to Medicsight, a commercial company offering lung cancer screening.

Aberle DR, Gamsu G, Henschke CI, Naidich DP, Swensen SJ (2001) A consensus statement of the Society of Thoracic Radiology: screening for lung cancer with helical computed tomography. *J Thorac Imaging* **16:** 65–8

Aoki T, Nakata H, Watanabe H et al (2000) Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. *AJR Am J Roentgenol* **174:** 763–8

Armato SG III, Giger ML, Moran CJ, Blackburn JT, Doi K, MacMahon H (1999) Computerized detection of pulmonary nodules on CT scans. *Radiographics* **19:** 1303–11

Armato SG III, Giger ML, MacMahon H (2001) Automated detection of lung nodules in CT scans: preliminary results. *Med Phys* **28:** 1552–61

Armato SG III, Li F, Giger ML, MacMahon H, Sone S, Doi K (2002) Lung cancer: performance of automated lung nodule detection applied to cancers missed in a CT screening program. *Radiology* **225:** 685–92

Black WC (2000a) Overdiagnosis: An underrecognized cause of confusion and harm in cancer screening. *J Natl Cancer Inst* **92:** 1280–2

Black WC (2000b) Unexpected observations on tumor size and survival in stage IA non-small cell lung cancer. *Chest* **117:** 1532–4

Brett GZ (1968) The value of lung cancer detection by six-monthly chest radiographs. *Thorax* **23:** 414–20

Cancer Research UK (2003) *CancerStats: Mortality – UK.* April 2003. Cancer Research UK, London

Department of Health (2000) *NHS Cancer Plan.* Department of Health, London (www.doh.gov.uk/cancer)

Diederich S, Wormanns D, Lenzen H et al (2000) Screening for asymptomatic early bronchogenic carcinoma with low dose CT of the chest. *Cancer* **89:** 2483–4

Diederich S, Wormanns D, Semik M et al (2002) Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. *Radiology* **222:** 773–81

Eddy DM (1989) Screening for lung cancer. *Ann Intern Med* **111:** 232–7

Ellis JR, Gleeson FV (2001) Lung cancer screening. *Br J Radiol* **74:** 478–85

Ellis SM, Husband JE, Armstrong P, Hansell DM (2001) Computed tomography screening for lung cancer: back to basics. *Clin Radiol* **56:** 691–9

Flehinger BJ, Melamed MR, Zaman MB, Heelan RT, Perchick WB, Martini N (1984) Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study. *Am Rev Respir Dis* **130:** 555–60

Fontana RS, Sanderson DR, Taylor WF et al (1984) Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. *Am Rev Respir Dis* **130:** 561–5

Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR (1986) Lung cancer screening: the Mayo program. *J Occup Med* **28:** 746–50

Fontana RS, Sanderson DR, Woolner LB et al (1991) Screening for lung cancer. A critique of the Mayo Lung Project. *Cancer* **67**(4 Suppl): 1155–64

Frost JK, Ball WC Jr, Levin ML et al (1984) Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. *Am*

KEY POINTS

- Low-dose chest computed tomography (CT) is a feasible method of diagnosing non-small cell lung cancer when it is still stage I.
- There is a high incidence of incidentally discovered small pulmonary nodules that require proper non-operative assessment to distinguish them from lung cancer.
- Studies of population screening for lung cancer by regular chest X-ray examinations have not shown a significant reduction in mortality from the disease.
- It is not yet known whether population screening for lung cancer using chest CT will reduce mortality from the disease.
- Determining whether population screening for lung cancer using CT does more good than harm at acceptable cost will require randomized trials.

Rev Respir Dis **130:** 549–54
Gohagan JK, Prorok JC, Kramer BS et al (1995) The prostate, lung, colorectal and ovarian screening trial of the National Cancer Institute. *Cancer* **75:** 1869–73
Hasegawa M, Sone S, Takashima S et al (2000) Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol* **73:** 1252–9
Heelan RT, Flehinger BJ, Melamed MR et al (1984) Non-small-cell lung cancer: results of the New York screening program. *Radiology* **151:** 289–93
Heffner JE, Silvestri G (2002) CT screening for lung cancer: is smaller better? *Am J Respir Crit Care Med* **165:** 433–4
Henschke CI, Yankelevitz DF (2000) CT screening for lung cancer. *Radiol Clin North Am* **38:** 487–95
Henschke CI, McCauley DI, Yankelevitz DF et al (1999) Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* **354:** 99–105
Henschke CI, Naidich DP, Yankelevitz DF et al (2001) Early lung cancer action project: initial findings on repeat screenings. *Cancer* **92:** 153–9
Henschke CI, Yankelevitz DF, Mirtcheva R et al (2002) CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol* **178:** 1053–7
Jemal A, Thomas A, Murray T, Thun M (2002) Cancer statistics, 2002. *CA Cancer J Clin* **52:** 23–47
Kaneko M, Eguchi K, Ohmatsu H et al (1996) Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology* **201:** 798–802
Kaneko M, Kusumoto M, Kobayashi T et al (2000) Computed tomography screening for lung carcinoma in Japan. *Cancer* **89**(11 Suppl): 2485–8
Kawakami S, Sone S, Takashima S et al (2001) Atypical adenomatous hyperplasia of the lung: correlation between high-resolution CT findings and histopathologic features. *Eur Radiol* **11:** 811–14
Ko JP, Betke M (2001) Chest CT: automated nodule detection and assessment of change over time - preliminary experience. *Radiology* **218:** 267–73
Kodama K, Higashiyama M, Yokouchi H et al (2002) Natural history of pure ground-glass opacity after long-term follow-up of more than 2 years. *Ann Thorac Surg* **73:** 386–92
Kubik A, Parkin DM, Khlat M et al (1990) Lack of benefit from semi-annual screening for cancer of the lung: follow-up report of a randomized controlled trial on a population of high-risk males in Czechoslovakia. *Int J Cancer* **45:** 26–33
Kubik AK, Parkin DM, Zatloukal P (2000) Czech study on lung cancer screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment. *Cancer* **89:** 2363–8
MacMahon H, Engelmann R, Behlen FM et al (1999) Computer-aided diagnosis of pulmonary nodules: results of a large-scale observer test. *Radiology* **213:** 723–6
Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR (2003) Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA* **289:** 313–22
Manser RL, Irving LB, Byrnes G, Abramson MJ, Stone CA, Campbell DA (2003) Screening for lung cancer: a systematic review and meta-analysis of controlled trials. *Thorax* **58:** 784–9
Marcus PM, Bergstralh EJ, Fagerstrom RM et al (2000) Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. *J Natl Cancer Inst* **92:** 1308–16
Marom EM, Sarvis S, Herndon JE, Patz EF Jr (2002) T1 lung cancers: sensitivity of diagnosis with fluorodeoxyglucose PET. *Radiology* **223:** 453–9
Miettinen OS (2000) Screening for lung cancer. *Radiol Clin North Am* **38:** 479–86
Miettinen OS, Henschke CI (2001) CT screening for lung cancer: coping with nihilistic recommendations. *Radiology* **221:** 592–6
Miller RR (1990) Bronchioloalveolar cell adenomas. *Am J Surg Pathol* **14:** 904–12
Mountain CF (1997) Revisions in the International System for Staging Lung Cancer. *Chest* **111:** 1710–17
Mulshine JL, Hirsch FR (2003) Lung cancer chemoprevention: moving from concept to a reality. *Lung Cancer* **41:** S163–174
Naruke T, Tsuchiya R, Kondo H, Asamura H (2001) Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: the Japanese experience. *Ann Thorac Surg* **71:** 1759–64
Nash FA, Morgan JM, Tomkins JG (1968) South London Lung Cancer Study. *Br Med J* **ii:** 715–21
Pastorino U, Bellomi M, Landoni C et al (2003) Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. *Lancet* **362:** 593–7
Patz EF Jr, Goodman PC, Bepler G (2000a) Screening for lung cancer. *N Engl J Med* **343:** 1627–33
Patz EF Jr, Rossi S, Harpole DH Jr, Herndon JE, Goodman PC (2000b) Correlation of tumor size and survival in patients with stage IA non-small cell lung cancer. *Chest* **117:** 1568–71
Patz EF Jr, Black WC, Goodman PC (2001) CT screening for lung cancer: not ready for routine practice. *Radiology* **221:** 587–91
Reeves AP, Kostis WJ (2000) Computer-aided diagnosis for lung cancer. *Radiol Clin North Am* **38:** 497–509
Rubin SA (1991) Lung cancer: past, present, and future. *J Thorac Imaging* **7:** 1–8
Sanderson DR (1986) Lung cancer screening. The Mayo Study. *Chest* **89**(Suppl): 324S
Smith IE (1999) Screening for lung cancer: time to think positive. *Lancet* **354:** 86–7
Sone S, Takashima S, Li F et al (1998) Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* **351:** 1242–5
Sone S, Li F, Yang ZG et al (2001) Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. *Br J Cancer* **84:** 25–32
Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R (2002) "Early" peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg* **74:** 1635–9
Swensen SJ, Jett J, Hartman TE, Midthun DE, Aughenbaugh GL, Sykes A (2002) Screening for lung cancer with CT: Mayo Clinic experience. *Radiology* **225:** 234
Swensen SJ, Jett JR, Hartman TE et al (2003) Lung cancer screening with CT: Mayo Clinic experience. *Radiology* **226:** 756–61
Tillich M, Kammerhuber F, Reittner P, Riepl T, Stoeffler G, Szolar DH (1997) Detection of pulmonary nodules with helical CT: comparison of cine and film-based viewing. *AJR Am J Roentgenol* **169:** 1611–14
Tockman MS (1986) Survival and mortality from lung cancer in a screened population. The John Hopkins Study. *Chest* **89**(Suppl): 324S–325S
Vazquez MF, Flieder DB (2000) Small peripheral glandular lesions detected by screening CT for lung cancer. A diagnostic dilemma for the pathologist. *Radiol Clin North Am* **38:** 579–89
Wang JC, Sone S, Feng L et al (2000) Rapidly growing small peripheral lung cancers detected by screening CT: correlation between radiological appearance and pathological features. *Br J Radiol* **73:** 930–7
Wilde J (1989) A 10-year follow-up of semi-annual screening for early detection of lung cancer in the Erfurt Country, GDR. *Eur Respir J* **2:** 656–62
Wormanns D, Diederich S, Lentschig MG, Winter F, Heindel W (2000) Spiral CT of pulmonary nodules: interobserver variation in assessment of lesion size. *Eur Radiol* **10:** 710–13
Wormanns D, Fiebich M, Saidi M, Diederich S, Heindel W (2002) Automatic detection of pulmonary nodules at spiral CT: clinical application of a computer-aided diagnosis system. *Eur Radiol* **12:** 1052–7
Yang ZG, Sone S, Takashima S, Li F, Honda T, Yamanda T (1999) Small peripheral carcinomas of the lung: thin-section CT and pathologic correlation. *Eur Radiol* **9:** 1819–25
Yang ZG, Sone S, Li F et al (2001a) Visibility of small peripheral lung cancers on chest radiographs: influence of densitometric parameters, CT values and tumour type. *Br J Radiol* **74:** 32–41
Yang ZG, Sone S, Takashima S et al (2001b) High-resolution CT analysis of small peripheral lung adenocarcinomas revealed on screening helical CT. *AJR Am J Roentgenol* **176:** 1399–407
Yankelevitz DF, Henschke CI (1997) Does 2-year stability imply that pulmonary nodules are benign? *AJR Am J Roentgenol* **168:** 325–8
Yankelevitz DF, Henschke CI (2000) Small solitary pulmonary nodules. *Radiol Clin North Am* **38:** 471–8
Yankelevitz DF, Gupta R, Zhao B, Henschke CI (1999) Small pulmonary nodules: evaluation with repeat CT – preliminary experience. *Radiology* **212:** 561–6
Zhao B, Yankelevitz D, Reeves A, Henschke C (1999) Two-dimensional multi-criterion segmentation of pulmonary nodules on helical CT images. *Med Phys* **26:** 889–95