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Proposals for lung cancer screening in the UK

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Lung cancer is the most frequent cause of cancer death in the Western world. Low dose Spiral CT offers a new approach to lung cancer detection and early results from screening studies are promising. United Kingdom proposals for a randomized controlled trial of lung cancer screening of spiral CT vs. a control arm of no screening is discussed.

Introduction

Lung cancer is now the leading cause of cancer death in the Western world and accounts for more deaths than the total from colon, lung and prostate cancer combined in the United States[1]. Although mortality from the disease has been declining over recent years, it remains the most common cause of cancer death in men, and in women mortality is second only to that of breast cancer. The vast majority (>90%) of cases are caused by cigarette smoking. Most patients present with advanced disease for which no curative treatment is available and only 8–14% of patients survive 5 years[2,3]. Therefore, novel approaches to the diagnosis and management of lung cancer are urgently required. Non-small cell lung cancer, which accounts for approximately 70% of all lung cancers, may benefit from screening and early detection because surgery for stage I disease results in 5-year survival rates ranging from 55% to over 80%[4,5].

Lung cancer screening

It is widely accepted that the only valid means of demonstrating the effect of lung cancer screening is by means of a randomized controlled trial with mortality from lung cancer as the primary end-point. Four randomized controlled trials of lung cancer screening were performed in the 1970s, all based on chest radiography together with sputum cytology[6–9]. None showed evidence of reduction in lung cancer mortality although none of the trials had sufficient statistical power to exclude a modest effect. The results of these trials formed the basis of the generally accepted view that lung cancer screening is ineffective.

The National Cancer Institute is reassessing the role of chest radiography in a large randomized controlled trial, the Prostate–Lung–Colorectal–Ovarian (PLCO) Trial, which is designed to have sufficient statistical power to identify a reduction in lung cancer mortality of 10%[10]. While chest radiography may identify lung lesions greater than 1 cm in diameter, Spiral CT can identify pulmonary nodules less than 5 mm in diameter. This has opened the way for the use of Spiral CT in early detection of peripheral lung cancers.

Early results from non-randomized trials in Japan and the United States using Spiral CT for screening lung cancer have shown that approximately four times as many tumours may be detected with Spiral CT than with conventional radiography. Most of these were stage I and are therefore likely to have a good prognosis[11–14]. The United States Early Lung Cancer Action Project (ELCAP) trial reported by Henschke *et al.*[14] enrolled 1000 subjects aged 60 years or over, with at least 10 pack years of cigarette smoking. Lung cancer was detected in 27 (2.7%) by CT and in seven (0.7%) by chest radiography; 23 (81%) had stage I disease at diagnosis. No cancers detected on chest radiography were missed on Spiral CT. Annual repeat Spiral CT detected a further seven interval cancers, all stage I[14]. Other studies from the Mayo Clinic and Germany have shown similar preliminary results. A recent report from Japan of a 3-year mass screening programme has demonstrated detection of nearly 11 times the expected annual number of early lung cancers[15].

Currently no randomized controlled trials are being conducted for lung cancer screening using Spiral CT as the intervention arm. The major issue regarding the design of randomized controlled trials (RCT) of Spiral CT is whether to use chest radiography or 'no screening' in the control arm. The major disadvantage of using chest radiography as the control arm is that the results of such an RCT would be difficult to interpret as the benefit of chest radiography, if any, is currently unknown. Furthermore, the control arm should represent standard practice and in most of the European studies, including the UK, standard clinical practice is 'no screening'.

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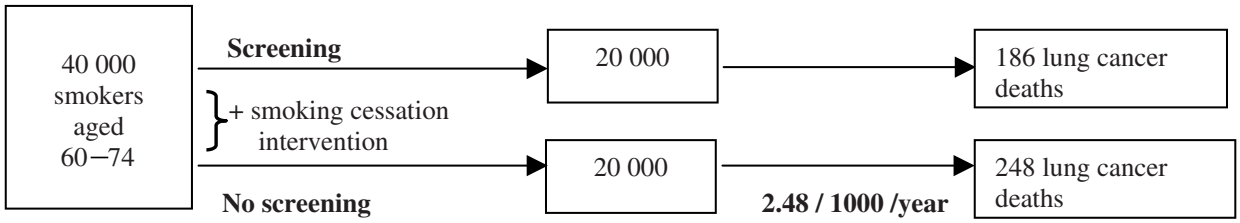

Figure 1 **UK Randomized Trial Design — for 5 years. The power to detect a difference of 25% at 5% level of statistical significance is 84%.**

While non-randomized controlled trials will provide information on the frequency of detection of malignant nodules with Spiral CT, none are designed to examine lung cancer mortality in a screened group in comparison with lung cancer mortality in a control group. Therefore, they will not answer the primary question 'does Spiral CT screening for lung cancer reduce lung cancer mortality?' In the United States there is increasing belief that Spiral CT for early lung cancer detection is likely to be beneficial, even in the absence of proven efficacy, and demand for this service is rapidly increasing. Thus randomized controlled trials of Spiral CT are timely. At the present time it is impossible to estimate the financial implications of screening but if Spiral CT is shown to be worthwhile, it is likely that the health impact would be as great or greater than that of breast cancer screening. Even if screening reduced lung cancer mortality by only 10% of all lung cancers, it would represent more than double the number of lives saved from breast cancer screening. The effect of Spiral CT screening may well be greater than 10%.

Spiral CT

Single-channel Spiral CT has been used in most of the low-dose screening studies to date. However, Multichannel CT, now being introduced widely into clinical practice, provides improved fast data acquisition combined with excellent image quality. This new CT technology is unlikely to be superseded by a significant alternative in the foreseeable future and is advocated for all proposed screening trials. It is important to use the most up-to-date technology because randomized controlled trials take many years to complete and advances in technology during the trial period may lead to criticism of the results.

Although the risk of X-radiation exposure is an important consideration, the dose of X-radiation received at Spiral CT screening is likely to be less than 2.5 mSv per scan, irrespective of the type of scanner used. Adopting the same protocol as Henschke *et al*.[14] and using a scanner of above-average dose efficiency, the patient dose is 1mSv[16]. This compares favourably with the average annual environmental exposure in the UK of 2.2 mSv, some regions receive as much as 10 mSv[16,17]. The radiation dose of Spiral CT will be monitored in a quality control programme by the physicist designated to the study.

The ELCAP study showed that 23% of individuals screened with Spiral CT had pulmonary nodules but only 2.7% of screened individuals had lung cancer, indicating a high ratio of benign to malignant nodules. False-positive Spiral CT examinations or false-positive histology/cytology results from biopsy may lead to unnecessary lung resection, introducing the risks of morbidity and mortality associated with thoracic surgery. However, in the ELCAP study no patient with a benign nodule was referred for thoracotomy. Biopsies were performed on 28 nodules and 27 of these were malignant[14]. Although risks of biopsy are small, they carry important clinical significance in elderly smokers with chronic obstructive pulmonary disease.

Small peripheral lung cancers may be missed on the initial Spiral CT examination although identified on a subsequent scan. Kakinuma *et al*.[13] reported that seven of 22 lung cancers were missed on initial screening with Spiral CT but when detected at follow-up, six of these were stage I. Lung cancers arising in the central airways are also likely to be missed on Spiral CT as the technique is insensitive in detecting small endo-bronchial lesions.

The proposed UK Spiral CT Trial

In the UK in 1999 lung cancer was responsible for 34 240 deaths (22% of all cancer deaths). Proposals for a randomized controlled trial have been developed by the UK Cancer Coordinating Committee for Research — Lung (UKCCCR). The primary research objective of the UK trial is to determine whether lung cancer screening using low-dose Spiral CT reduces mortality from lung cancer. To address this issue a randomized controlled trial of Spiral CT vs. no screening in smokers, 60 years and over, is proposed, with lung cancer mortality as the primary end-point. Smoking cessation will be offered to both the screened and unscreened group. Initially a pilot trial of 2000 individuals is planned, the purpose of which is to determine the feasibility, compliance and costs of a large randomized controlled trial. There will be six participating centres in the pilot.

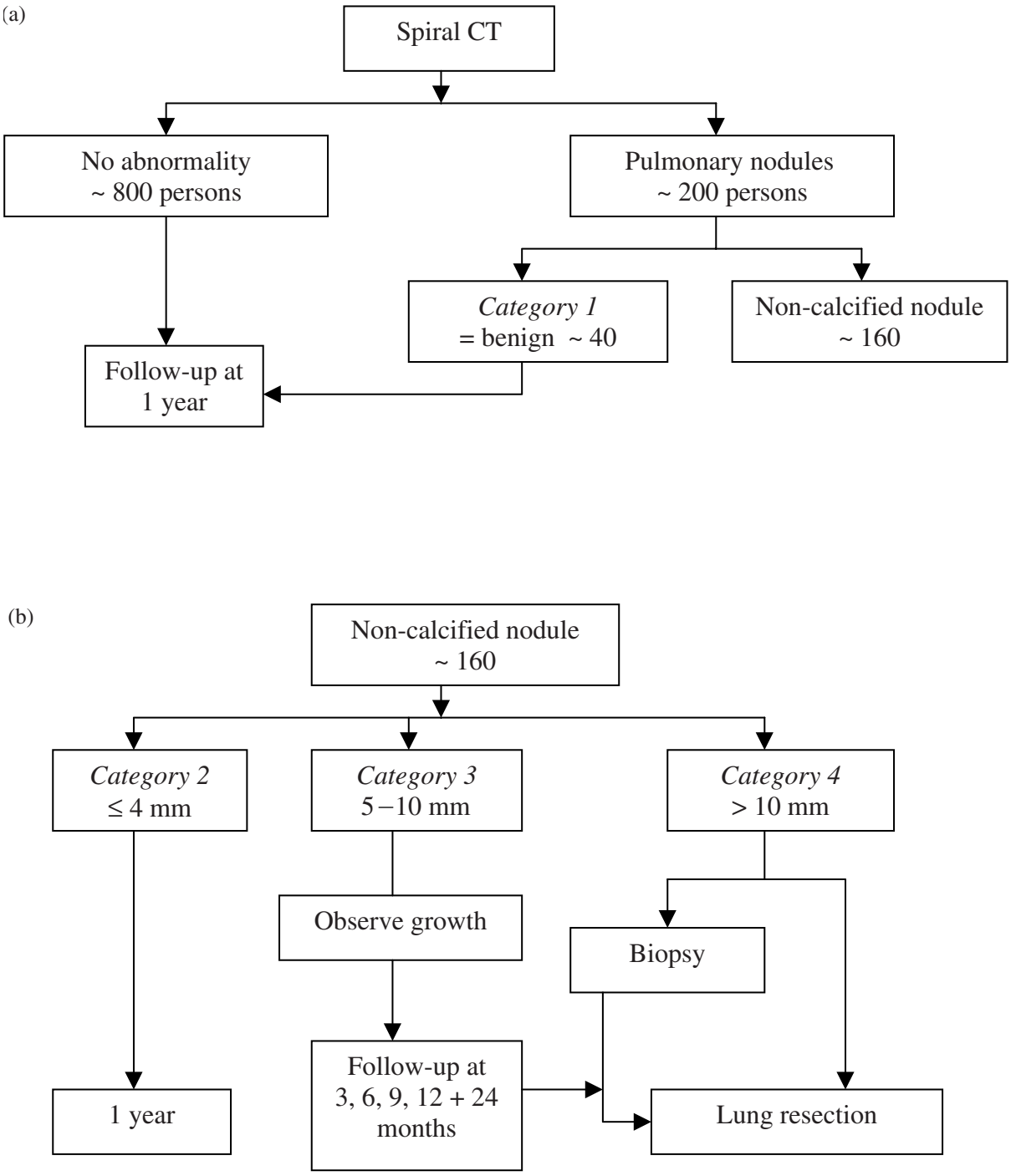

Figure 2 **Algorithm for evaluating lung nodules.**

It is anticipated that approximately 40 000 individuals will be required in the full trial conducted over 5 years to demonstrate a reduction in lung cancer mortality of 25%. In the pilot we propose to perform Spiral CT at baseline and then at 1 year. In the full trial Spiral CT would be performed annually for 5 years (Fig. 1).

The success of the pilot will be based upon the ability to identify eligible individuals for the trial, the number recruited, and their return for a second Spiral CT scan after 1 year. This information will be used to determine the size, duration and costs of the full trial, provided the pilot is considered to be successful. In addition, the pilot will indicate the proportion of subjects who have

nodules which require further evaluation and the proportion of these that are cancers including observation of nodule growth. The algorithm for evaluating nodules is shown in Fig. 2.

Definition and classification of nodules

A pulmonary nodule is defined as soft tissue or ground glass opacity of rounded shape.

Category 1

Benign nodules: lesions showing central, rim, uniform or other benign distribution of calcification; fat attenuation within the nodule, clear linear or linear branching densities, or known to be stable size for at least 12 months (for CT, defined as within measurement error of up to $\sim$20%).

Category 2

Micronodules, i.e. $\leq$4 mm diameter. The characteristics and locations of all nodules will be documented for purposes of future comparison at annual screening CT.

Category 3

Indeterminate nodules of 5–10 mm diameter whose growth rate is, as yet, undetermined, which do not fall into Category 1.

Category 4

Nodules >10 mm diameter which do not fall into the description for benign nodules, or those <10 mm if known to be enlarging on serial CT studies. Nodule characteristics may include round or spiculated margins, and cavitation. Focal areas of ground glass are also included in this category.

All Category 3 nodules will be measured and observed for tumour growth at 3, 6, 9, 12 and 24 months.

Nodule measurement

Soft tissue nodules are be measured (in mm) on standard lung and soft tissue windows, as defined above, using the maximum short axis (x) and long axis (y) diameters taken at the widest point of the nodule. Tumour volume can be calculated from the 2-dimensional measurements using the prolate eclipse formula (dimension $x \times$ dimension $y \times 0.52$).

Recent research using specially designed computer software (Nodview) developed by Dr A Reeves and colleagues[18] at the Weill Medical College of Cornell University, New York, USA, has shown that tumours are frequently irregular in shape and may also grow asymmetrically. This new software, which is currently still under development, promises to be considerably more accurate for assessing tumour growth.

Conclusion

Lung cancer screening is being investigated throughout the Western world using low-dose Spiral CT and some encouraging results have already been published. A randomized controlled trial is generally accepted as the only method of demonstrating a reduction in disease-specific mortality. However, as yet, no randomized trials of lung cancer screening are being conducted. Proposals for a UK randomized controlled trial of Spiral CT vs. no screening are presented.

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Colon cancer screening

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Colorectal cancer is a major health problem worldwide. Last year in the United States alone, more than 130 000 people were diagnosed with colorectal cancer and more than 56 000 died of their disease[1]. Fortunately, this neoplasm is highly suited to screening because of its long preclinical phase, during which it is detectable and curable[2]. Nevertheless, screening programs for colorectal cancer have been only partly successful, owing largely to poor patient compliance with screening recommendations[3,4]. A number of organizations including the World Health Organization (WHO), the American Cancer Society (ACS), the Agency for Health Care Policy and Research (AHCPR), the US Preventive Service Task Force (USPSTF), and the American Gastroenterology Association (AGA) have issued or endorsed guidelines for colorectal cancer screening. This review summarizes the clinical evidence supporting colorectal cancer screening in the average-risk population and in high-risk groups, discusses the advantages and disadvantages of the available screening tests, and outlines the currently recommended guidelines for screening based on risk category.

Average-risk population

Average-risk patients are asymptomatic individuals aged 50 years of age or older who have no personal or family history of colorectal cancer or adenomatous polyps and no history of in ammatory bowel disease. The two most recently published screening recommendations, those of the ACS[5] and AHCPR[6], present guidelines for screening average-risk patients in the form of lists of options (Table 1). The options include annual fecal occult blood test (not included as a stand alone test in the ACS guidelines), exible sigmoidoscopy every 5 years, annual fecal occult blood test plus exible sigmoidoscopy every 5 years, double-contrast barium enema every 5 to 10 years, and colonoscopy every 10 years.

Table 1 Recommended options for colorectal cancer screening in asymptomatic, average-risk individuals*

Starting at age 50
Annual FOBT†
Flexible sigmoidoscopy every 5 years
Annual FOBT and sigmoidoscopy every 5 years
Colonoscopy every 10 years
Double-contrast barium enema every 5–10 years

*Winawer SJ, Fletcher RH, Miller L *et al*. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112: 594–642.
†The American Cancer Society does not recommend fecal occult blood testing (FOBT) by itself.

Fecal occult blood testing

Fecal occult blood testing (FOBT) is the safest and least expensive of the currently available screening tests. Three prospective, randomized, controlled trials have demonstrated the effectiveness of FOBT in reducing colorectal cancer mortality by 15% to 33%[7–9]. However, its benefit in reducing colorectal mortality is attributed not only to early cancer detection but also to the incidental discovery and removal of adenomatous polyps at subsequent colonoscopy. Such chance discovery of adenomatous polyps and non-bleeding cancers by colonoscopy has been estimated to account for 16–25% of the colorectal cancer deaths prevented by the use of FOBT[10]. Limitations of FOBT include its relatively low sensitivity for detecting cancers and its inability to detect the vast majority of adenomas[11]. Because colorectal cancers bleed intermittently, 50% or more of patients with colorectal cancer may have a negative test result[11,12]. Thus, to be effective, FOBT must be administered annually or biennially, which makes patient compliance a problem. Furthermore, the positive predictive value of FOBT is only approximately 10%[11,12].