SHORT COMMUNICATION

Overview of observational studies of low-dose helical computed tomography screening for lung cancer

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Objective: Lung cancer is a substantial public health problem in Western countries. Evidence from previous controlled trials of chest radiography and sputum cytology does not support lung cancer screening, but computed tomography (CT) screening has recently emerged as a more sensitive screening tool. For the present article, the available observational studies of low-dose helical CT screening for lung cancer were reviewed.

Methodology: An evidence-based review of all published observational studies of low-dose helical CT screening for lung cancer, identified by an extensive search of Medline, was conducted.

Results: Eight observational studies of CT screening for lung cancer were identified. Relative to chest radiography, low-dose helical CT is a sensitive screening tool and can detect a high proportion of small lung cancers at an early and resectable stage. The yield of sputum cytology in addition to CT screening appears to be relatively low. To date, 5-year lung cancer survival of all individuals participating in baseline screening has not been reported for any of the studies.

Conclusions: Although these preliminary studies are very promising, it remains to be proven that the early detection and treatment of lung cancer will lead to a reduction in mortality. This issue will be addressed by randomized controlled trials. In the interim, the long-term follow up of these observational studies could provide further insights.

Key words: computed tomography, lung neoplasm, mass screening.

INTRODUCTION

Lung cancer is the commonest cause of cancer death in most developed countries.1 The case fatality rate is high and most individuals are diagnosed only once they have advanced disease, for which therapeutic options are limited.2 Early detection trials conducted in the 1970s failed to show a reduction in lung cancer mortality but this could relate to the relatively poor sensitivity of chest radiography with or without sputum cytology.3–7 The superior sensitivity of helical computed tomography (CT) screening for lung cancer has recently been demonstrated in observational studies, but randomized controlled trials are needed to determine whether screening will lead to a reduction in lung cancer mortality.8,9 Survival statistics from screened cohorts can be affected by biases such as selection bias, length time, lead time and overdiagnosis bias, and therefore survival data from uncontrolled studies cannot be used to establish effectiveness.10,11 However, observational studies can provide data on test accuracy, feasibility
and acceptability, and any improvements in survival noted in uncontrolled-screened cohorts could be further evaluated in randomized controlled studies with mortality as the outcome of interest. It has been argued that if CT screening is effective, a ‘stage shift’ would be expected so that among a screened group there would be not only more patients with early stage disease, but also fewer with advanced disease compared with unscreened populations. Although previous controlled lung cancer screening trials failed to show a reduction in mortality, there was an increase in the proportion of early stage cancers detected by screening, but no reduction in the absolute number of late stage cancers in the screened cohort. This finding is consistent with overdiagnosis bias.

The potential role for researchers in the evaluation of this rapidly evolving technology was the subject of a recent Australian National Cancer Control Initiative report. An extensive search of electronic databases was conducted as outlined elsewhere. In 2003, the Medline search was updated to include a search for both controlled and uncontrolled trials of lung cancer screening from 1995 onwards. Observational studies of CT screening were excluded from the Cochrane review; however, all the published studies identified by this search are reviewed in the present article. No attempt was made to identify or include unpublished data.

IDENTIFICATION AND SELECTION OF STUDIES FOR REVIEW

The authors of the present review had previously conducted a Cochrane systematic review of controlled trials for the early detection of lung cancer. An extensive search of electronic databases was conducted as outlined elsewhere. In 2003, the Medline search was updated to include a search for both controlled and uncontrolled trials of lung cancer screening from 1995 onwards. Observational studies of CT screening were excluded from the Cochrane review; however, all the published studies identified by this search are reviewed in the present article. No attempt was made to identify or include unpublished data.

DESCRIPTION OF STUDIES

Eight observational studies of low-dose helical CT screening were identified in the updated literature search (up to August 2003). Several of these had more than one citation. The key features and results of uncontrolled CT screening studies are summarized in Tables 1–3. Further details about the individual studies are provided in the text below. Each of the studies adopted slightly different protocols for the evaluation of suspicious lesions, but in general, abnormalities detected on screening with low-dose CT were followed up with high-resolution thin-section CT. For the present report, specificity was calculated by classifying all positive initial low-dose CT scans prior to further evaluation with high-resolution thin-section CT as a positive, and the results described refer to those cancers detected by CT scanning but not those detected by sputum cytology alone. There was no gold standard (apart from follow-up) that could be used to calculate sensitivity. False-negatives were those lung cancers that were missed or not visible at baseline screening but were detected either by symptoms, or at repeat screening (at a 2-year or shorter interval), or by sputum cytology alone.

Anti-Lung Cancer Association Project

The Anti Lung Cancer Association is a profit-based organization and screening was offered to due-paying participants. Screening CT scans, classified as showing either benign tumour, active inflammatory disease, or suspected lung cancer, were reviewed by an additional radiologist to determine the necessity for thin-section CT. Detailed CT was recommended when the findings showed a solitary nodule without calcification, a nodule >4.9 mm in diameter, or an area of localized opacification increasing in size on sequential imaging. After 1996 a computer-aided diagnosis system was used. Positive results were more common in the later years of the study as diagnostic criteria were revised. Lung cancers missed at the initial screening were described in a separate report (up to 1996). As at February 2001, overall and lung-cancer-specific 5-year survival of screen-detected cases was 71.0 and 85.5%, respectively.

Hitachi Employees Health Insurance Group

In this ongoing study, helical CT scanning was offered to employees during annual health examinations. The exact recruitment procedure and the number of individuals offered screening was not described. Over three-quarters of participants were less than 60 years old, but the mean age was not reported. When screening identified non-calcified solitary pulmonary nodules (SPN) of ≥8 mm, a detailed CT scan was carried out 1 month later. For nodules ≥11 mm, biopsy was recommended. SPN 8–10 mm in diameter were examined with detailed CT scans 3 months and 6 months later. If there had been no growth, annual screening was recommended. For nodules 5–7 mm in diameter, annual routine screening was recommended. Of the 2099 participants with nodules at baseline screening, 541 were encouraged to undergo a detailed CT scan. The number of nodules detected at repeat screening was not described, but 148 individuals were referred for a detailed CT.

Finnish Institute of Occupational Health Study

In this study, baseline screening only was conducted on 602 construction workers who were recruited (with a participation rate of 94%) from a prior study of asbestos-related occupational disease. Eighty-five individuals (including 20 non-smokers) had asbestosis and 601 had bilateral pleural plaques. For nodules detected by CT, fine-needle aspiration biopsy was undertaken when malignancy could not be ruled out and where lesions were suitable. Otherwise follow-up CT was recommended. Surgery was indicated for
Table 1  Observational CT screening studies: methods and study population

<table>
<thead>
<tr>
<th>Institution, Country</th>
<th>Year started</th>
<th>( n )</th>
<th>Population</th>
<th>Mean age; median age (years)</th>
<th>Men (%)</th>
<th>Never smokers (%)</th>
<th>CT scanning (all helical)</th>
<th>Low-dose CT slice thickness (mm)</th>
<th>No. radiologists reading each CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Center Research Institute,† Japan(^{19})</td>
<td>1993</td>
<td>1611</td>
<td>Fee paying members</td>
<td>40–80</td>
<td>88</td>
<td>14</td>
<td>120 kVp, 50 mA, pitch 2:1</td>
<td>10</td>
<td>2 (prior to 1996)</td>
</tr>
<tr>
<td>Hitachi Health Care Center, Japan(^{21})</td>
<td>1998</td>
<td>7956</td>
<td>Hitachi employees</td>
<td>50–69</td>
<td>79</td>
<td>38</td>
<td>120 kVp, 50 mA, pitch 2:1</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Shinshu University, Japan(^{19})</td>
<td>1996</td>
<td>5483</td>
<td>General population</td>
<td>40–74; 64</td>
<td>54</td>
<td>54</td>
<td>Mobile CT: 120 kVp, 50 mA, pitch 2:1</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Cornell University, USA(^{19,14})</td>
<td>1992</td>
<td>1000</td>
<td>High-risk volunteers</td>
<td>≥60; 67</td>
<td>54</td>
<td>0(^{1})</td>
<td>140 kVp, 40 mA, pitch 2:1</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Mayo Clinic, USA(^{20})</td>
<td>1999</td>
<td>1520</td>
<td>High-risk volunteers</td>
<td>50–85; 59</td>
<td>52</td>
<td>0(^{1})</td>
<td>Multislice CT: 120 kVp, 40 mA, pitch 1.5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>University of Münster Germany(^{16})</td>
<td>1995</td>
<td>817</td>
<td>High-risk volunteers</td>
<td>40–78; 53</td>
<td>72</td>
<td>0(^{1})</td>
<td>120 kVp, 50 mA, pitch 1.5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>University of Milano, Italy(^{22})</td>
<td>2000</td>
<td>1035</td>
<td>High-risk volunteers</td>
<td>50–84; 58</td>
<td>71</td>
<td>0(^{1})</td>
<td>140 kVp, 40 mA, pitch 2</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Finnish Institute of Occupational Health, Finland(^{23})</td>
<td>Late 1990s (not stated)</td>
<td>602</td>
<td>Workers with prior asbestos exposure</td>
<td>38–81; 63</td>
<td>98</td>
<td>3</td>
<td>140 kVp, 125 mA, pitch 1.5</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^{1}\)And National Cancer Center Hospital and Social Health Insurance Medical Center, Tokyo, National Cancer Center Hospital East, Chiba, Gifu University School of Medicine, Gifu and Shikoku Cancer Center, Ehime, Japan, for the Anti-Lung Cancer Association.

\(^{2}\)Each of these studies enrolled current and ex-smokers (median pack years 40–45).

CT, computed tomography; kVp, kilovolt peak; mA, milliangstrom.
<table>
<thead>
<tr>
<th>Institution</th>
<th>Nodules or positive screen ($n$ (%))</th>
<th>Lung cancers ($n$ (%))</th>
<th>Non-small-cell; adenocarcinoma (%)</th>
<th>Stage I; stage IA (%)</th>
<th>Sensitivity; specificity (%)</th>
<th>Cancers missed or misclassified by CT</th>
<th>Cancers detected by sputum cytology alone</th>
<th>No. benign non-surgical biopsies</th>
<th>No. benign surgical biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Center Research Institute,† Japan18</td>
<td>186 (11.5)</td>
<td>18 (0.81)</td>
<td>100; 71</td>
<td>77; 69</td>
<td>65; 89</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hitachi Health Care Center, Japan23</td>
<td>2099 (26.4)</td>
<td>36 (0.44)</td>
<td>100; 95</td>
<td>86; 78</td>
<td>92; 74</td>
<td>3</td>
<td>Not tested</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Shinshu University, Japan19</td>
<td>279 (5.1)</td>
<td>22 (0.40)</td>
<td>100; 83</td>
<td>100; 91</td>
<td>55; 95</td>
<td>17</td>
<td>1</td>
<td>Not reported</td>
<td>7</td>
</tr>
<tr>
<td>Cornell University, USA2,14</td>
<td>233 (23.0)</td>
<td>30 (3.00)$^\ddagger$</td>
<td>100; 79</td>
<td>85; 81</td>
<td>86; 78</td>
<td>3</td>
<td>Not tested</td>
<td>Not reported§</td>
<td>4$^\ddagger$</td>
</tr>
<tr>
<td>Mayo Clinic, USA2,18</td>
<td>782 (51.0)</td>
<td>26 (1.70)</td>
<td>93; 70</td>
<td>76; 68</td>
<td>96; 49</td>
<td>0</td>
<td>1</td>
<td>Not reported§</td>
<td>8$^\ddagger$</td>
</tr>
<tr>
<td>University of Münster Germany16</td>
<td>350 (43.0)</td>
<td>11 (1.30)</td>
<td>92; 50</td>
<td>58; 50</td>
<td>Not assessed; 58</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not tested</td>
<td>1</td>
</tr>
<tr>
<td>University of Milano, Italy23</td>
<td>214 (21.0)</td>
<td>11 (1.06)</td>
<td>100; 91</td>
<td>55; 55</td>
<td>65; 80</td>
<td>6</td>
<td>Not tested</td>
<td>Not reported§</td>
<td>5</td>
</tr>
<tr>
<td>Finnish Institute of Occupational Health, Finland21§</td>
<td>111 (18.4)</td>
<td>5 (0.80)</td>
<td>100; 40</td>
<td>40;</td>
<td>100; 82</td>
<td>0</td>
<td>Not tested</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

$^\dagger$And National Cancer Center Hospital and Social Health Insurance Medical Center, Tokyo, National Cancer Center Hospital East, Chiba, Gifu University School of Medicine, Gifu and Shikoku Cancer Center, Ehime, Japan, for the Anti-Lung Cancer Association.

$^\ddagger$Includes three non-nodule-associated cancers.

$^\ddagger$Four biopsies for benign disease were performed (none were lobectomies) but further details were not provided.

$^\ddagger$This figure covers both baseline screen and first annual repeat screen as reported in 2003.

CT, computed tomography.
Table 3  Repeat CT screening: results of first repeat screening

<table>
<thead>
<tr>
<th>Institution</th>
<th>National Cancer Center Research Institute(^{18})</th>
<th>Hitachi Health Care Center(^{23})</th>
<th>Shinshu University(^{19})</th>
<th>Cornell University(^{14})</th>
<th>Mayo Clinic(^{20,24})</th>
<th>University of Milano(^{22})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval</td>
<td>6 months</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual</td>
</tr>
<tr>
<td>No. screened (no. examinations)</td>
<td>789(^{1})</td>
<td>5568</td>
<td>4425</td>
<td>841 (first repeat screen) + 343 (second repeat screen)</td>
<td>1478 (first repeat screen) + 1438 (second repeat screen)</td>
<td>996</td>
</tr>
<tr>
<td>Adherence with screening (%)</td>
<td>74(^{1})</td>
<td>70</td>
<td>83</td>
<td>88</td>
<td>98(^{1})</td>
<td>96</td>
</tr>
<tr>
<td>No. cancers detected by CT</td>
<td>19(^{1})</td>
<td>4</td>
<td>27(^{1})</td>
<td>7(^{1})</td>
<td>10(^{1})</td>
<td>11</td>
</tr>
<tr>
<td>No. non-small-cell cancers</td>
<td>18(^{1})</td>
<td>4</td>
<td>25</td>
<td>6(^{1})</td>
<td>10(^{1})</td>
<td>11</td>
</tr>
<tr>
<td>No. adenocarcinomas</td>
<td>14(^{1})</td>
<td>4</td>
<td>24</td>
<td>5(^{1})</td>
<td>5(^{1})</td>
<td>7</td>
</tr>
<tr>
<td>Cancers stage I (%)</td>
<td>83(^{1})</td>
<td>100</td>
<td>89</td>
<td>83(^{1})</td>
<td>60(^{1})</td>
<td>100</td>
</tr>
<tr>
<td>No. cancers detected by sputum cytology alone</td>
<td>Not tested</td>
<td>None</td>
<td>Not tested</td>
<td>1(^{1})</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Not described</td>
<td>Insufficient data available</td>
<td>83</td>
<td>Insufficient data available</td>
<td>Insufficient data available</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Specificity</td>
<td>91(^{1})</td>
<td>97</td>
<td>97</td>
<td>97(^{1})</td>
<td>Insufficient data available</td>
<td>90</td>
</tr>
<tr>
<td>No. non-surgical biopsies or bronchoscopies for benign disease</td>
<td>23(^{1})</td>
<td>1</td>
<td>Not described</td>
<td>1(^{1})</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td>No. surgical biopsies for benign disease</td>
<td>4(^{1})</td>
<td>2</td>
<td>5</td>
<td>1(^{1})</td>
<td>8(^{5})</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^{1}\)Covers all repeat screens reported (reported as a composite).

\(^{1}\)With first repeat screen.

\(^{1}\)Includes two cases that were initially misclassified on CT (false-negatives).

\(^{1}\)See Table 2 (covers baseline and repeat screenings). CT, computed tomography.
large tumours or when growth of a nodule was suspected. Non-suspicious nodules were followed up with CT. False-negatives were identified by searching the National Cancer Registry 3 years after screening finished and therefore sensitivity might have been overestimated.\textsuperscript{21} Five lung cancers were identified (two of which were visible only on CT and not by chest radiography). None of the participants survived disease-free. However, two of the three individuals with operable cancer did not undergo surgery—one because of delayed diagnosis.\textsuperscript{21}

**Early Lung Cancer Action Project**

This is an ongoing study of annual CT screening in high-risk individuals.\textsuperscript{8,14} Screening CT was recorded as positive if between 1 and 6 non-calcified nodules were detected. Nodules were classified as benign if they had benign calcification with smooth edges and were less than 20 mm in size.\textsuperscript{8} Individuals with non-calcified nodules were referred for standard-dose, diagnostic CT scan and those with a benign pattern of calcification were classified as benign. For non-calcified nodules 5 mm or less in diameter, follow-up high-resolution CT was recommended at 3 months, and if there had been no growth, CT was repeated at 6, 12 and 24 months. Non-calcified nodules between 6 and 10 mm in diameter were dealt with on an individual basis with either biopsy or follow-up CT. Non-calcified nodules 11 mm or more in size were referred for biopsy.\textsuperscript{8} At baseline, 27 lung cancers were diagnosed (only seven of these were also detected by chest radiography).\textsuperscript{19} A further three endobronchial or mediastinal lung cancers were detected by CT.\textsuperscript{8} Repeat ‘annual’ screening was performed 6–18 months after the previous screen.\textsuperscript{14} The sensitivity of CT screening (at baseline) for all lung cancers (nodule and other) was 86% (30/35). If a positive result was classified as a positive detailed CT scan, then the specificity at baseline for nodule-associated cancer was 90%. If a positive result was classified as any positive screening CT then the specificity was 78%.\textsuperscript{8}

**The Mayo Clinic Study**

This American study is ongoing. Results of baseline screening and first annual repeat screenings were reported in 2002 and updated to include information on second annual repeat screenings in 2003.\textsuperscript{24} Almost all participants were white; 49% were previous Mayo Clinic patients.\textsuperscript{8} Follow-up standard-dose CT scans were performed at external institutions. Nodules were managed by attending physicians according to recommendations made by the investigating team.\textsuperscript{20} Recommendations were based on an algorithm developed by the investigators.\textsuperscript{20} For nodules less than 3 mm in diameter, thin-section CT was recommended at 6 months, and for 3–7-mm nodules, thin-section CT was recommended at 3 months. For 8–20-mm nodules, thin-section CT was recommended as soon as possible. During 3 years of annual screening, 40 lung cancers were diagnosed and the mean size of non-small-cell lung cancers was 15 mm.\textsuperscript{24} After 3 years of annual screening, 696 additional abnormalities that required further evaluation were identified.\textsuperscript{24}

**University of Münster Study**

The results of baseline screening have been reported for this German study, but further annual repeat screening is planned.\textsuperscript{16} Nodules 10 mm or less in size were followed with a repeat limited thin-section low-dose CT at 3 months. If growth had occurred at 3 months, biopsy was performed. Otherwise further follow-up CT scans were performed at 6, 12 and 24 months. Nodules greater than 10 mm in size were evaluated on an individual basis and those with morphological features of malignancy were biopsied, whereas others were followed with a repeat thin-section CT at 3 months.\textsuperscript{16} The prevalence of non-calcified nodules after assessment with thin-section low-dose CT was unchanged. There were 12 lung cancers diagnosed in 11 individuals and 92% were resectable at diagnosis.\textsuperscript{16} After a mean follow up of 27 months, 55% of subjects were alive with no evidence of recurrent lung cancer.\textsuperscript{16}

**Shinshu University Study**

Mobile helical CT screening was offered to members of the general population in rural Japan.\textsuperscript{8,19} Individuals (n = 5483) were screened in 1996 and repeat annual screens were performed in 1997 (n = 4425) and 1998 (n = 3878). Diagnostic work-up (including high-resolution thin-section CT) was recommended for individuals with screening CT scans showing non-cancerous suspicious lung lesions, suspicion of lung cancer, or small lung nodules (<3 mm in diameter).\textsuperscript{18} When the high-resolution CT scan did not strongly suggest cancer, a re-examination was recommended at 3, 6, 12, 18 and 24 months. The investigators stated that the interpretation of images was based on commonly used morphological and density characteristics and interval changes of the lesion but further details were not provided.\textsuperscript{19} The sensitivity was better at the first annual repeat screening than at baseline screening. Of the 60 cancers diagnosed, 73% were less than 15 mm in size.\textsuperscript{19}

**Istituto Nazionale Tumori and University of Milan**

In this ongoing annual screening study, positron emission tomography (PET) was included in the diagnostic algorithm, and follow-up CT scanning of nodules 5 mm or smaller was deferred until 12 months.\textsuperscript{22} Non-calcified lesions larger than 5 mm were referred for limited thin-section CT within 1 month, with assessment of contrast enhancement where appropriate.\textsuperscript{22} Lesions showing positive enhancement (>30 Hounsfield units), positive PET scan, or non-calcified lesions 20 mm or larger were candidates for biopsy. At baseline screening, 61 individuals were recalled for high-resolution CT (five revealed benign
Almost all (95%) of the 22 lung cancers detected were resectable. In three of six cases with a benign surgical biopsy, the PET finding was the main indication for biopsy. Six cancers diagnosed at repeat screening were identified at baseline CT, but all were stage I at diagnosis, with a median size of 11.6 mm compared with 5.5 mm at baseline.

**DISCUSSION**

Relative to chest radiography, low-dose helical CT is a sensitive screening tool for lung cancer and can detect a high proportion of small lung cancers at an early and resectable stage. The yield of sputum cytology in addition to CT screening appears to be relatively low. Three studies have now reported systematic follow up of the cohort of individuals screened at baseline. In the screened cohorts, the proportion of early to late stage cancers is high compared with those presenting in practice, but further follow up is required to confirm this. For several studies, systematic follow up of all individuals screened at baseline has not yet been reported. In the absence of systematic follow up, the data on test accuracy, stage distribution and survival should be interpreted with caution. To date, 5-year lung cancer survival of all individuals taking part in baseline screening has not been reported for any of the studies.

The majority of studies of high-risk individuals recruited participants through advertising or hospital clinics and therefore selection bias could exist. The two largest studies were conducted on lower-risk populations and it is unlikely that these results could be generalized to high-risk populations. Interestingly, both studies on low-risk populations found a relatively high prevalence of lung cancer (especially adenocarcinoma or bronchioloalveolar carcinoma) among non-smokers and, assuming adequate ascertainment of smoking history, this could partly be a reflection of length-biased sampling and possibly overdiagnosis. In fact, the predominance of adenocarcinomas among these screened cohorts in general could reflect selection and overdiagnosis bias. It will be interesting to observe if this persists with prolonged follow up.

Computed tomography screening is an evolving technology. The CT techniques used vary between studies and the methods used to define and investigate abnormalities also differ. Only three of the studies reported the effective radiation dose used in their screening CT. Diederich et al. reported a radiation dose of 0.6 mSv in men and 1.1 mSv in women. Only one study adequately assessed interobserver agreement and described excellent agreement among experienced chest radiologists (kappa statistic 0.91). As might be expected, there appears to be a trade-off between sensitivity and specificity. Specificity was poorest in the two studies that used 5-mm CT slice thickness, but the Mayo Clinic study also demonstrated a very high sensitivity at baseline. However, in studies using 10-mm slice thickness, it appears that many lesions missed or misclassified at baseline screening were subsequently identified at repeat screening, and the majority of these were still stage I or IA tumours. Indeed, Pastorino et al. showed that the repeat evaluation of lesions measuring up to 5 mm could be deferred until 12 months with minimal risk of progression.

Nonetheless, a high false-positive rate is a fairly consistent feature of these studies and this is likely to be a major limitation of CT screening. The prevalence of fungal granulomas among different populations is thought to be one factor that could contribute to a high false-positive rate in endemic areas. But, as the Mayo Clinic study investigators pointed out, despite a high false-positive rate in their study, only two of the eight benign lesions excised were granulomas. Most studies reported a low rate of surgical biopsy of false-positive nodules, but this might be higher outside the clinical trial setting. Although serial imaging of smaller indeterminate nodules can be used to limit the number of biopsies for benign disease, benign nodules can show radiological evidence of nodule growth, whereas 22% of cancers have doubling times of 465 days or greater. Furthermore, although the selective use of PET scanning can reduce the duration of diagnostic evaluation and therefore alleviate some anxiety among participants, it might not further reduce the benign biopsy rate substantially.

The Early Lung Cancer Action Project investigators reported a very low rate of biopsy for benign disease in association with a relatively high sensitivity and specificity, but this has yet to be replicated by other investigators. Concerns have recently been raised about the potential cost-effectiveness of screening, and analysis suggests that a sizeable stage shift will be necessary for screening to be cost-effective. Ultimately, as with many screening programmes, many individuals must be screened for the benefit of a few. The burden and benefits of screening need to be evaluated carefully with attention to both mortality and quality of life, and long-term assessment of the impact of false-positive results. Although these preliminary studies are very promising, it remains to be proven that the early detection and treatment of lung cancer will lead to a reduction in mortality. This issue will be addressed by randomized controlled trials. In the interim, the long-term follow up of these observational studies could provide further insights. Randomized controlled trials of CT screening need to be conducted using standardized and reproducible approaches to the performance and interpretation of CT scans and the evaluation of abnormal results, so that any research findings can be implemented broadly to ensure appropriate access.

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REFERENCES


