Progress in Lung Cancer Screening  
—CT screening and the diagnosis of small lung cancers—

JMAJ 46(12): 525–531, 2003

Akinobu YOSHIMURA

Lecturer, 4th Department of Internal Medicine, Nippon Medical School

Abstract: Several case-control studies on lung cancer screening conducted in Japan reported that the current screening method contributes to the reduction of the risk of lung cancer death. However, the effectiveness has not been established, since randomized controlled trials (RTCs) in other countries did not confirm the effectiveness of screening in reducing lung cancer death rates. Because further improvement of accuracy is not expected using chest X-rays, studies were conducted to evaluate the possibility of low-dose helical CT as a new method of lung cancer screening. The results indicate that CT screening achieves a higher detection rate and detects a larger number of early-stage lung cancers. An advantage in survival rate was also reported. A cohort study is ongoing in Japan to evaluate the effectiveness of CT screening in reducing lung cancer deaths. While the widespread use of CT screening improved the detection of small lung cancers, diagnosis still requires thoracoscopic or open lung biopsy. It is necessary to develop low-invasive methods for the diagnosis of small lung cancers.

Key words: Lung cancer screening; Low-dose helical CT; Case-control study; Cohort study; Small lung cancer

Introduction

Lung cancer screening is conventionally performed using radiography of the chest. These methods have largely reached the limit of technical progress. There is a consensus that detection of early-stage lesions is difficult even using double reading and comparative reading protocols to improve diagnostic performance. Chest CT is superior to conventional radiography in density resolution, and it avoids the problem of blind spots caused by the overlapping of structures such as the heart, diaphragm, and bones in radiography. Despite these advantages in lesion detection, chest CT has not been used in screening because of the problems of exposure dose and long scanning time.

In 1990, a system was developed in which the
X-ray tube moves continuously along a spiral during the acquisition of projection data (Fig. 1). This technique shortened the time required for scanning. In the chest region, imaging of the whole lungs can now be performed with a 15-second breath hold, and this method is considered suitable for use in screening. With respect to exposure dose, satisfactory diagnostic performance is obtained when the current is reduced from the conventional value of 150 mA to 50 mA. Many facilities are now examining the possibility of lung cancer screening using low-dose high-speed helical CT (CT screening).

**Present State of Lung Cancer Screening**

Indirect chest radiography has been used in Japan since before World War II, initially for tuberculosis screening. The focus of screening shifted from tuberculosis to lung cancer, reflecting the changes in the prevailing disease profile. This procedure was covered by the Elderly Health Law in 1987, and standardized...
screening protocols were defined in “The Manual of Mass Screening for Lung Cancer” and “The Manual of Clinic-based Lung Cancer Screening Program” to promote lung cancer screening.3,4) Later, the subsidies for cancer screening were placed into the framework of the general revenue (to be covered by a portion of national tax revenue allocated to local governments) in fiscal 1998, and cancer screening became a non-mandatory service conducted by municipalities. The efficacy of lung cancer screening has not been established, since randomized controlled trials (RCTs) in other countries evaluating lung cancer screening did not confirm the effectiveness in decreasing lung cancer death rates.5–8) Six case-control studies have been conducted in Japan (Fig. 2).9–13) Sobue et al. reported that the estimated 0.72 reduction in the risk of death was indicative of the efficacy of screening, although the value was not statistically significant.9) Okamoto et al. reported a significant decrease in the risk of lung cancer death in their report on clinic-based screening.10) Based on these results, it was concluded that the current method of lung cancer screening contributes to the reduction of the risk of lung cancer death, provided that appropriate accuracy management is performed.11)

Lung Cancer Screening Using Low-Dose Helical CT

It is generally acknowledged that lung cancer screening using chest X-ray has little room for further improvement of diagnostic accuracy. As discussed above, the development of low-dose helical CT made it possible to shorten scanning time and reduce exposure dose, and this technique has been evaluated as a new method of lung cancer screening.12)

The development of CT units for lung cancer screening started in 1990 in Japan. Preliminary evaluation was conducted to establish the basic design concept and to perform risk, benefit, and cost analyses. Following these efforts, CT

<table>
<thead>
<tr>
<th>Table 1 Results of CT Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>


c) Repeated screening at intervals of several months.
d) Median of tumor diameter.
screening came to be practiced widely. An initial screening study covering 5,483 inhabitants of Nagano prefecture detected 23 cases of lung cancer with a detection rate of 0.42%, and all cases were stage I (Table 1). The results of initial screening conducted by the Anti-Lung Cancer Association (ALCA), a membership organization conducting lung cancer screening in high-risk groups in Tokyo, and the Early Lung Cancer Action Project (ELCAP) in the U.S.A. indicated detection rates of 0.87% and 2.7%, respectively, and the percentage of stage I cases was 79% and 85%, respectively (Table 1). CT screening showed detection rates that were 4 to 8 times as high as that of the chest X-ray conducted simultaneously. A summation of the data from 8 facilities performing over 1,000 cases of CT screening reproducibly demonstrated the superiority of this method: detection rate was 0.36% and the percentage of stage I cases was 79%. Sobue et al. also reported excellent results in which the 5-year survival of the lung cancer patients detected by initial screening and repeated screening was 76.2% and 64.9%, respectively.

However, a problem associated with CT screening is the high percentage of cases requiring diagnostic workup. The high rate of false-positive cases means a large number of persons receiving unnecessary workup, and we need to address this problem in view of the aggressiveness of diagnostic examination, the psychological burden on the patients, and the increase in medical expenditure. Future improvement is expected to take place through the preparation of interpretation standards and guidelines for small lung cancers, training and experience of evaluating physicians, and the introduction of comparative reading systems.

Survival rates are confounded with 4 types of biases: (1) length bias, (2) self-selection bias, (3) lead time bias, and (4) overdiagnosis bias. The overdiagnosis bias (the fact that some of the cancers detected by screening do not lead to the death of the patient) presents a major problem in the case of CT screening, because this technique is characterized by high detection rates and a high percentage of adenocarcinomas among detected lung cancers. As a result, some of the patients incorrectly diagnosed as having lung cancer undergo unnecessary treatment.

Although CT screening is expected to improve survival rates, evaluation based on survival rates is not appropriate for evaluation of the effectiveness of CT screening in decreasing lung cancer death rates. The group for “the study on the identification of groups with high cancer prevalence and the early diagnosis and treatment to improve prognosis” (leader: Takichiro Suzuki) was organized under Health Science Research Grants for Medical Frontier Strategy Research for the purpose of conducting cohort studies to evaluate the efficacy of CT screening. It is necessary to confirm the efficacy in reducing lung cancer death rates before using this method for lung cancer screening in the general population.

**Diagnosis of Small Lung Cancers**

The widespread use of CT screening increased the detection of “small lung cancers” with diameters of 15mm or less (Table 1). Most of these cancers are adenocarcinomas of peripheral origin. On high-resolution CT, small lung cancers appear as ground-glass opacities, solid opacities, or mixtures of these lesions, and they are characterized by the involvement of bronchi and blood vessels and air bronchograms (Fig. 3). The observed characteristics of these lesions are considered to correlate with Noguchi’s classification of small lung adenocarcinomas based on histopathological analysis.

Although imaging diagnosis of small lung cancers is making progress, definitive diagnosis still requires pathological or cytological confirmation. Transbronchial or percutaneous lung biopsy under X-ray fluoroscopy guidance is not useful for the evaluation of opacities that are...
not identified by chest X-ray. At present, diagnosis of small lung cancers is considered difficult. Suspected lung cancer lesions are generally examined by CT (fluoroscopy) guided transbronchial or percutaneous lung biopsy. If diagnosis is not given by these procedures, thoracoscopic or open lung biopsy is performed. In practice, surgical diagnosis is needed in many cases. Ten out of 14 cases (71%) of small lung cancers with diameters of 15 mm or less needed thoracoscopic or open lung biopsy for definitive diagnosis at our facility. It is necessary to develop low-invasive methods for the diagnosis of small lung cancers.

On the other hand, nodular opacities lacking evidence of malignancy are followed up without invasive diagnosis. There are no guidelines stipulating the intervals and duration of follow-up. Aberle et al. proposed that nodular opacities smaller than 10 mm in diameter should be followed up at 3, 6, 12, and 24 months, while those with diameters of 10 mm or more should be diagnosed by biopsy. It is necessary to establish appropriate guidelines for follow-up based on a sufficiently large number of cases.

**Conclusion**

Case-control studies in Japan suggest the effectiveness of lung cancer screening. However, the effectiveness has not been established, since randomized controlled trials in other countries did not confirm the efficacy in reducing lung cancer death rates. The development of low-dose helical CT made it possible to consider CT screening as a new method of lung cancer screening. This technique is promising in lung cancer screening because of its ability to detect early-stage lung cancers that have a good chance of cure. However, it is necessary to confirm the efficacy in reducing lung cancer death rates before using this method for lung cancer screening in the general population. Diagnosis of small lung cancers requires CT guided transbronchial or percutaneous lung biopsy in some cases and thoracoscopic or
open lung biopsy in others. Surgical diagnosis is needed in many cases. It is necessary to develop low-invasive methods for the diagnosis of small lung cancers.

REFERENCES


20) Yoshimura, A., Ando, M., Kudo, S. et al.:


