How Can We Detect Curable Early Lung Cancers?

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Lung cancer is the leading cause of cancer mortality worldwide. In 2006, 45941 men and 17314 women died from lung cancer in Japan. Despite modest improvements in the treatments for lung cancer during the last few decades, the over-all 5-year survival rate still remains approximately 15%. Therefore, to reduce the number of deaths from this lethal disease, the early detection followed by definitive treatment is essential.

Annual chest X-ray has been the usual screening procedure for the early detection for lung cancer. However, several randomized controlled trials (RCTs) during the 1970s failed to demonstrate a reduction in lung cancer mortality by means of screening with chest radiography[1]. The Mayo Lung Project[2] was the largest RCT among them. In this study, 9212 participants were randomized to a screening group, which underwent annual chest X-ray and sputum cytology every 4 months, and to a non-screening control group. After 9 years, the number of detected lung cancer was significantly higher in the screening group than that in a control group (p=0.013), whereas there were no significant differences in lung cancer mortality between the 2 groups (p=0.62). On the basis of these results, screening for lung cancer has been considered to have no effect on the reduction of cancer mortality in the United States. However, with the recent advances in radiology, the efficacy of lung cancer screening is still under intense investigation. In this article, I review some recent trials for the early detection of lung cancer and discuss the interpretation of the results.

Japanese Experiences

Despite the negative results of RCTs in the United States, annual screening with chest X-ray still continues in Japan. Several Japanese case-control studies during the 1990s demonstrated that lung cancer screening contributed, to some extent, to the reduction of cancer mortality[3)~6)]. In Okayama Prefecture, annual chest X-ray and sputum cytology for high-risk participants have been conducted. Nishii *et al.*[3] compared 412 individuals who died of lung cancer with 3490 controls as to their screening histories. The smoking-adjusted odds ratio of death from lung cancer for screened individuals versus unscreened individuals within 12 months prior to diagnosis was calculated to be 0.59 (95% confidence interval: 0.46-0.74; p=0.0001). They concluded that lung cancer screening contributes to the reduction of lung cancer mortality by 41%. Table 1 shows the summary of other case-control studies. These results demonstrated that screening

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Table 1. Case-control studies of lung cancer screening in Japan

Authors	Prefecture	No. of cases	No. of adjusted controls	OR (95%C.I.)
Nishii *et al.*[3]	Okayama	412	3490	0.59 (0.46-0.74)
Sagawa *et al.*[4]	Miyagi	328	1886	0.54 (0.41-0.73)
Tsukada *et al.*[5]	Niigata	174	801	0.40 (0.27-0.59)
Nakayama *et al.*[6]	Gunma	121	536	0.68 (0.44-1.05)

C.I.=confidence interval

with chest X-ray could reduce the risk of death from lung cancer by 32-60%. Based on these data, annual screening with chest X-ray for all the participants and sputum cytology for high-risk populations are recommended in "Guidelines for Lung Cancer Screening" in Japan (Grade B). However, it should be noted that the efficacy of screening can be achieved only with sophisticated quality control and successive annual screenings.

CT Screening for Lung Cancer

In 1996, Kaneko *et al.*[7] demonstrated, for the first time, the efficacy of lung cancer screening with low-dose spiral computed tomography (CT) scanning. They performed CT screening twice a year from 1993 to 1995 for 369 individuals (which accounted to a total of 3457 examinations) at a high risk of lung cancer, and detected 15 cases of lung cancer. It is worth to note that the detection rate of 0.43% was 10-fold higher than that of conventional screening by chest X-ray, and that 11 (73%) of 15 tumors were undetectable with chest radiography. Fourteen (93%) of 15 tumors were diagnosed as stage I, and were completely resected. After this sensational report, several investigators in the United States launched feasibility studies for CT screening. Henschke *et al.*[8] demonstrated that pulmonary nodules were detected in 233 (23%) of 1000 symptom-free volunteers who underwent low-dose CT screening, and 27 cases (2.7%) were diagnosed as lung cancer. Of the 27 CT-detected lung cancers, 26 (96.3%) were resectable. Swensen *et al.*[9] also reported the results of low-dose CT screening in Mayo Clinic. They demonstrated that 40 cases of lung cancer were detected among 1520 participants (2.6%), and 21 (60%) of 35 non-small cell lung cancer (NSCLC) detected with CT were at stage IA. The mean size of the CT-detected lung cancers was 15mm. The results of several studies on baseline CT screening are summarized in Table 2[10)~13)]. These results showed that CT screening could increase the detection rate of lung cancer, and that a majority of CT-detected lung cancers were in the early stage. However, the efficacy of CT screening in reducing cancer mortality still remains controversial. Bach *et al.*[14] compared the results of 3 single-arm studies of CT screening with those of validated prediction models. They demonstrated that although CT screening for lung cancer might increase the rate of lung cancer diagnosis (relative risk (RR) 3.2; 95%CI 2.7-3.8) and the possibility of surgical resection (RR 10.0; 95%CI 8.2-11.9), there were no significant differences in mortality from lung cancer between the CT-screening

Table 2. Studies of low-dose CT screening

Institution	No. of positive results (%)	No. of lung cancers (%)	Stage I (%)
ELCAP, US [8]	233 (23)	27 (2.7)	88
I-ELCAP, international [10]	NR	405 (1.3)	86
Mayo Clinic, US [9]	1049 (69)	40 (2.6)	60
ALCA, Japan [11]	186 (12)	13 (0.8)	77
Univ. of Milano, Italy [12]	61 (6)	11 (1.1)	55
PALCAD, Ireland [13]	109 (24)	2 (0.4)	100

ELCAP=Early Lung Cancer Action Project
ALCA=Anti-Lung Cancer Association
PALCAD=ProActive Lung Cancer Detection
NR=not reported

groups and control models (RR 1.0; 95%CI 0.7-1.3). Because survival is the most appropriate measure for the evaluation of medical interventions, we should be cautious when interpreting these conflicting results.

Biases Affecting the Results of Screening Studies

There are 3 distinct biases that affect the comparison between survival in screening-detected cases and that in clinically detected cases.

1. Lead-time Bias

When survival is calculated from the time of diagnosis, the comparison between screening-detected cases and clinically detected cases is influenced by the lead-time bias. Even when early detection followed by treatments has no real effect on the length of survival from the day of carcinogenesis, screening will appear to prolong survival by the lead-time (Fig.1).

2. Length Bias

Cases detected by annual screening are more likely to be slowly progressive than those that develop between annual screenings and are clinically present. In fact, a majority of CT-detected lung cancers were adenocarcinomas, which are known to have a long doubling time, whereas small cell lung cancer was rarely detected by screening. Therefore, screening-detected cases show better prognosis because of the slowly progressive behavior of its own.

3. Overdiagnosis Bias

Overdiagnosis bias does not indicate the false-positive diagnosis of benign diseases, but the

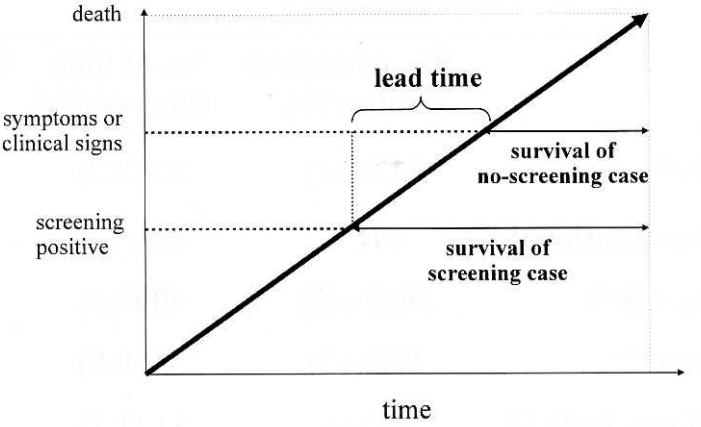

Fig. 1. Lead time bias.
Without screening, diagnosis is made when clinical symptoms develop. With screening, the diagnosis is advanced by the lead time which is a period from the detection on screening to the time when the symptom occurs. Even when the early detection has no real effect on the length of survival, screening will appear to prolong survival by the lead time.

overestimation of diseases that are unlikely to cause critical symptoms or death during the patient's lifetime. Some investigators have claimed that even though a significantly high number of lung cancers were detected by CT-screening, the cancer mortality was not reduced probably because of overdiagnosis bias.

Ongoing Randomized Controlled Trials

To eliminate these biases, RCTs are considered the best method for determining the efficacy of any intervention. Presently, 2 large RCTs are being conducted.

National Lung Screening Trial (NLST) is being conducted by the National Cancer Institute (NCI). From August 2002 to April 2004, 53464 participants were recruited in the United States, and were randomized to undergo screening for 3 years with either low-dose CT or chest X-ray. The primary endpoint is lung cancer mortality of the participants in each group 6 years after randomization. The results will be reported in 2010.

The NELSON trial is being conducted in the Netherlands and Belgium. From 2003 to 2005, 15428 participants were randomized to a CT-screening group or a non-screening group. The study is designed to detect lung cancer mortality reduction 10 years after randomization.

CONCLUSION

Decrease in the lung cancer mortality by regular screening has not been conclusively proven yet. The results of 2 large abovementioned RCTs are expected to solve this uncertainty in a few years. However, the most important thing for us is to be careful not to overlook the faint signs of lung cancer on chest X-rays or CT scans taken in the daily medical examinations. I believe this is the most realistic way of detecting curable lung cancers at their early stage.

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