

Present Strategy of Lung Cancer Screening and Surgical Management

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Previous lung cancer screening trials in the United States (US) employing chest X ray and sputum cytology did not demonstrate reductions in lung cancer mortality. However, recent case control studies in Japan demonstrated a decrease in lung cancer mortality in the computed tomography (CT) screened group. Lung cancer screening using chest CT detected more cancers at an earlier stage than chest X ray. Before CT screening is widely performed, lung cancer mortality reduction should be proved in a scientific manner. The problem of a much higher false positive rate of this method should be solved. The subtypes of adenocarcinoma; bronchioloalveolar carcinoma (BAC) tends to show specific CT findings called ground glass opacity (GGO) and a favorable prognosis can be expected. BAC is usually invisible by chest X ray and detected only by CT. Recent studies have shown the proportion of GGO is strongly related to biological malignancy of small adenocarcinoma. Based on this fact, thoracic surgeons wish to identify the possibility of limited resection for minimally invasive cancers. Lung cancer researchers are interested in evaluating the nature of small adenocarcinoma as well as the carcinogenic process. A comprehensive understanding of screening-detected cancers including the CT images, pathology and genetic analysis is necessary for optimum management of such nodules. (Ann Thorac Cardiovasc Surg 2005; 11: 363–6)

Key words: lung cancer screening, computed tomography screening, ground glass opacity, limited surgery

Lung Cancer Screening: Past and Present

Lung cancer is the primary cancer killer worldwide due to delayed diagnosis. The five year survival rate is less than 15% for those with lung cancer. However, ~80% of stage IA cases survive more than five years. Early detection may be the best way to improve prognosis. Mass

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screening is a strategy for early detection. However, the effect in decreasing lung cancer mortality has not been demonstrated. Three randomized controlled trials (RCTs) in the United States (US) (Mayo, Johns Hopkins, Memorial-Sloan Kettering) screened high risk individuals using chest X ray and sputum cytology in the 1980's and failed to show reduction of lung cancer mortality.¹⁻⁵⁾

Since these pessimistic results were reported, public lung cancer screening has not been recommended. Recently, fair quality case-control studies in Japan showed lung cancer mortality benefit using chest X ray and sputum cytology⁶⁻¹¹⁾ (Table 1). These results might be due to good quality control as well as improvement of diagnosis and treatment of detected cancer compared to those of 20-30 years ago. However, as those studies were retrospective, a recommendation for screening could not be made.

Table 1. Case control study of lung cancer screening in Japan

Group (ref.)	Method	No. of		% of screened		odds ratio (95% CI)
		cases	controls	cases	controls	
Miyagi ¹¹⁾	x-p+sp	328	1,886	73.5	82.6	0.54 (0.41-0.73)
Okayama ⁸⁾	x-p+sp	412	3,490	32.3	43.9	0.59 (0.46-0.74)
Niigata ⁹⁾	x-p+sp	174	801	35.0	56.2	0.40 (0.27-0.59)
Gunma ¹⁰⁾	x-p	121	536	57.9	67.2	0.68 (0.44-1.05)

Case: died of lung cancer between the age of 40 and 79.

Table 2. Lung cancer screening using low-dose spiral CT

Author (ref.)	No. of cases	Age	% of cancer	% of stage I
Sobue ¹³⁾	1,611	40-79	0.87	78
Sone ¹⁴⁾	5,483	40-74	0.4	100
Nawa ¹⁶⁾	7,956	50-69	0.44	89
Henschke ¹²⁾	1,000	60-	2.5	83
Swensen ²³⁾	1,520	50-85	2.7	85

It is reported that the sensitivity of chest X ray is low in detecting early stage lung cancer. The application of chest computed tomography (CT) to screening was firstly performed by the Anti-Lung Cancer Association (ALCA) in Tokyo. Much higher sensitivity in detection of lung cancer, especially in localized cases, was reported. Recently, a number of studies suggest that CT screening may increase the lung cancer detection rate by 3-10 times compared with chest X ray and that 70-80% of detected cancers are stage I¹²⁻¹⁶⁾ (Table 2). The prevalence of lung cancer in each study might change according to the risk (smoking status, age, etc.) of subjects. However, the mean tumor size is less than 2 cm in each study and it is obvious most of such cases survive longer than those detected by chest X ray.

The question has been evoked whether CT screening decreases lung cancer mortality.

The preclinical stage of lung cancers detectable by CT screening should be much earlier than that of cancers detected by chest X ray. Evaluation based on survival will be biased by lead-time bias and length-bias. To evaluate the efficacy of CT screening, prospective randomized control trials have started in the US and Europe. The end-points of these trials are mortality reduction. The National Lung Screening Trial (NLST) sponsored by National Cancer Institute (NCI) has been scheduled to accrue 50,000 current and former smokers with age range of 55-74. These are randomized to chest X ray group versus spiral CT group and will be followed up until 2009.

Reduction of lung cancer mortality in the CT group will be analyzed. In Netherlands, a total of 20,000 high risk individuals will be randomized to undergo chest CT or standard care (NELSON trial). Such a randomized trial is not being performed in Japan. However, a large scale prospective cohort study of CT screening has already started and mortality rates due to lung cancer will be analyzed based on the data of 50,000 subjects.

Small Cancers Detected by CT Screening

Most small cancers detected by CT screening are adenocarcinomas. Based on high resolution CT findings, small adenocarcinoma is usually classified into three groups; Solid type, Mixed type and ground glass opacity (GGO) type. Bronchioloalveolar carcinoma (BAC) seldom shows abnormalities on chest X ray because it grows without destroying alveolar structure. Lung cancers with a large GGO component tend to be BAC or minimally invasive adenocarcinomas which have good prognoses.¹⁷⁾ The Noguchi's classification is routinely used to classify the subtypes of small adenocarcinomas (Table 3).¹⁸⁾ Type A and B are considered to be non-invasive cancer and Type D, E, F, to be invasive cancer. Cases with enormous proportion of GGO tend to be type A or B and have a favorable prognosis. Hence, the solid dominant cancers tend to be types D, E, F and have a poor prognosis. There are several reports indicating that the ratio of the size of GGO and that of consolidation on the high resolution computed

Table 3. Noguchi's classification and lymph node involvement

	Nodal meta. (%)
A: Localized BAC (LBAC)	0
B: LBAC with foci of collapse of alveolar structure	0
C: LBAC with foci of active fibroblast proliferation	28.4
D: Poorly differentiated adenoca.	47.7
E: Tubular adenoca.	55.6
F: Papillary adenoca. with destructive growth	25
<i>Cancer 1995</i>	

tomography (HRCT) is strongly related to the stage and prognosis.¹⁹⁻²²⁾

Intervention on the Non-calcified Nodule

The biggest potential difficulty in CT screening has been reported to be a higher false positive rate compared to that of chest X ray. Non-calcified nodules were detected in 15-50% of all screens.^{12-16,23)} Most of these were followed up and had invasive diagnostic procedures as the protocol required, which often showed negative for malignancy. The follow-up and/or invasive procedure causes physical and emotional discomfort. The definitive protocol for diagnostic work-up should be established. The sophisticated algorithm of intervention of International Early Lung Cancer Action Program (IELCAP) is shown in their website.²⁴⁾

Surgery for Screening Detected Cancer

Lobectomy and locoregional lymph node dissection have been recommended as standard lung cancer operation procedures. This is based on the fact that nearly 20% of adenocarcinomas less than 2 cm in diameter were reported to be node positive and 5% of cases less than 1 cm were also N1 or N2 disease.²⁵⁻²⁸⁾ Also, the Lung Cancer Study Group failed to demonstrate positive results of limited resection for clinical T1 lung cancers. The limited surgery group showed a local recurrence rate 5-6 times higher than the lobectomy group.²⁹⁾ However, many thoracic surgeons postulated that GGO dominant cases might be candidates for limited resection. The Noguchi's classification is useful in evaluating the aggressive potential in individual cases, but these criteria are based on postoperative pathologic findings and could not have a strong impact on the choice of treatment. Therefore we need criteria which are available preoperatively to define early mini-

mally invasive cancers. Lesser resection mainly for GGO dominant tumors showed favorable results in some registry studies.^{30,31)} Also, the Japan Clinical Oncology Group (JCOG) recruited resected T1 cases to analyze the relationship between CT findings and pathological results including lymph node metastasis as well as nodal and vascular involvement. The results of these studies may contribute to reveal characteristics of minimally invasive tumors which can be cured by limited resection. Small cancers with a high GGO ratio might be candidates for limited resection, however, prospective randomized studies comparing lobectomy versus limited resection will be necessary to confirm this.

Comprehensive research including pathology, CT images and molecular analysis are needed to define non-invasive adenocarcinoma and will alter conventional method of management of tiny cancers. We are in the midst of a historic evolution of the study of lung adenocarcinoma, which was triggered by CT screening.

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