Lung cancer screening using low-dose CT

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Lung cancer is the leading cause of death from cancer among men and women in the United States. Despite new diagnostic techniques, the overall five-year survival rate remains about 14% and most patients still present with advanced disease. There has long been interest in screening to detect lung cancers when they are smaller and presumably at earlier and more curable stages, as witnessed by the support for previous screening trials using chest radiography and cytologic examination of sputum. Unfortunately, these trials failed to reach the ultimate goal of a diagnostic screening test, i.e. a decrease in disease-specific mortality. The screened groups had the same number of deaths from lung cancer as the control groups, and screening was effectively abandoned. With the development of helical CT and at present time multislice CT scanner, there has been a resurgent interest in screening for lung cancer. Data obtained from subjects at the time of study entry (prevalence-screening data) from recent trials using low-dose CT suggest that this technique could save lives in persons at high risk.

Non randomised trials

Two non-randomized studies from Japan used chest radiography, low dose CT, and examination of a 3-day pooled sputum sample for screening. These trials enrolled 9544 people more than 40 years of age (1, 2). The Early Lung Cancer Action Project (ELCAP), performed in New York, enrolled 1000 high-risk smokers over the age of 60 years. This trial has a nonrandomized design and uses chest radiography and low dose CT (3). In 1999, the Mayo Clinic enrolled 1520 current or formers smokers (≥ 50 years old who had smoked 20 pack/years or more) in a nonrandomized trial. All the patients underwent base-line low dose CT and sputum cytologic examination and they will have an annual follow-up for 3 consecutive years. A trial at the University of Munster in Germany enrolled 919 participants all smokers over the age of forty (4). The results of these trials have confirmed that CT is more sensitive than conventional chest radiography for the detection of lung nodules and that some of these nodules prove to be lung cancer (Table 1). For instance in the ELCAP study, CT detected more cases of lung cancer (27% vs 9.1%) than chest radiography and more patients screened by CT have resectable early stage disease (3). In the Mayo Clinic study, 24 cases of lung cancer have been diagnosed with 21 (14%) prevalence and 3 incidence cases (1.3%). In the Munster study, 13 lung cancers were depicted (14%), 8 (62%) of whom had a stage I disease (4).

Table 1. Results of nonrandomized trials in lung cancer screening using low dose CT

	USA (New York)	Japan	USA (Mayo Clinic)	Germany (Muenster)
No of subjects	1000	9544	1500	919
Age	>60	>40	≥50	>40
Cancer detected	27	53	21	13
Detection rate	2.7%	0.56%	1.4%	1.4%
Stage 1	85%	80%	50%	62%

Limitation of nonradomised trials

Cancer screening programs should do more good than harm, at a financial cost acceptable to society. To be good means to extend quality of life (QALY) and reduce mortality from the tumor. To do harm means to induce complications of the screening test, anxiety due to lead-time and consequences of false positive diagnoses.

The true clinical significance of the small tumors found by screening is unknown and their effects on mortality waits for future investigation (4). Given the data from simple arm studies performed in Japan, the United States and Germany, it is plausible (but unproved) that earlier detection

of lung cancer will likely result in decreased mortality. It is not clear at what price this will occur. The biases induced by the screening program are important to consider.

The lead-time bias expresses that a reduction in survival from a cancer is not the same as mortality. A cancer detected earlier by a screening test may lead to the death of the patient at the same time it would occur if the tumor was not detected. Because of the lead-time bias, a screening test that increases the survival time does not imply a reduced mortality.

The length-time bias is defined by the tendency of a screening test to detect slow-growing or less invasive lesions than those detected in non screening populations. Such tumors often have a better, sometimes excellent, prognosis.

The selection bias is due to the tendency of health conscious people to volunteer for (or to maneuver themselves into) a screening program. Such people adhere to treatment advice and are generally healthier.

The over-diagnosis bias is related to the diagnosis by histopathologists of benign lesions or *in situ* cancers as invasive carcinomas. Pathologists find multiple "lung tumors" in 5 - 20% of lobectomy specimens from patients with stage I lung cancers, which they classify as adenomatous hyperplasia or bronchioloalveolar adenomas. These two processes are believed to be precursors of invasive lung cancers.

Volume doubling times of lung cancer is longer (1 - 40 months, mean 15 months) in CT program than chest radiography (1 - 18 months, mean 5 months). The size of the nodule at diagnosis does not necessarily correlate with the clinical outcome. In a recent study of 510 patients with T1N0M0 disease (tumors less than 3 cm in diameter), there was no statistical correlation between small size at diagnosis and survival (5). Patients with 3-cm masses had the same outcomes as those with nodules less than 1 cm in diameter. Tumors may already have demonstrated their potential to remain localized or to metastasize by the time they are visible on CT imaging. In some studies, about 60% of patients with clinical stage I disease (radiographically detected; tumors less than 3 cm in diameter) died from lung cancer within five years despite appropriate therapy. This suggests that a high percentage of patients have disseminated, occult disease at the time of presentation. It is important to recognize that even a 10-mm lung cancer is not an earlier lung cancer; 10-mm lung cancer has approximately doubled thirty times and is in the last third of the expected time life of lung cancer. Finally, a recent experimental study showed that a 1-cm tumor can shed approximately 3 million to 6 million cells into the blood every 24 hours.

False positives

In addition to detecting an increased number of lung cancers, low dose CT found at least one undetermined nodule in 39-50% of all screened patients. The majority of these nodules should be benign, but evaluation of all these nodules is not a trivial problem. This could create a very expensive diagnostic strategy. Consequences (costs) of false positive diagnoses have also to be taken into consideration (anxiety, unnecessary further imaging, biopsy or even surgery, complications of investigation and financial outcomes). Morbidity and mortality considerations are particularly disconcerting in cases of benign lesions and overdiagnosed cancers. In the Mayo Clinic trial, 2244 uncalcified lung nodules were identified in 60% of 1520 participants. The authors estimate that approximately 98% of these are falsely positive findings. Assuming that their 13% incidence rate of undetermined lung nodules continues, almost all patients will have at least one false positive examination after only a few years of screening.

Randomized controlled trials

They eliminate lead-time, length and selection biases, but they are very difficult to set up. Contamination is a major problem. They take a very long time to produce definite results and in the interval technology changes and their results may not be relevant when trial finally reports.

Several groups are now proposing prospective randomized controlled trials using low dose CT. In the US, one cooperative group organized by the American College of Radiological Imaging Network (ACRIN), sponsored by the National Cancer Institute (NCI) has designed a multicenter randomized controlled trial involving 80 000 participants over five years which should have the power to detect a 20% reduction in mortality. This project is based on 2 arms: the screening group would be examined by annual low dose CT, the control group will be examined by annual chest radiograph. It is now funded and should start next year. Other projects of randomized trials have been designed in Europe. Although there are some differences in inclusion criteria and arms, there is a potential

opportunity to pool the data and reinforce the power of the results. A European coordination has been established on this matter under the umbrella of the European Society of Thoracic Imaging and the European Association of Radiology. For the moment, only pilot studies (1000 patients for 2 years) have been funded in two countries (France and Denmark).

The recommended lung nodule management algorithm is designed to expedite surgery for lung cancer and minimize intervention for benign nodules (Tables 2 and 3).

Table 2. Definition and classification of nodules in lung cancer screening program

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 a least 12 months (for CT, defined as within measurement error of up to ~20%).

Category 2. Micronodules ie: (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 tumor growth at 3, 6, 9, 12 and 24 months.

Table 3. Nodule measurement recommendation in lung cancer screening trials program

1. Soft tissue nodules are be measured (in mm) on standard lung and soft tissue windows, using the maximum short axis (X) and long axis (Y) diameters taken at the widest point of the nodule. Tumor volume can be calculated from the 2 dimensional measurements using the prolate eclipse formula (dimension X x dimension Y x 0.52).

2. Recent research using specially designed computer softwares have shown that tumors are frequently irregular in shape and may also grow asymmetrically. These new softwares, which are currently still under development, and not completely validated promise to be considerably more accurate for assessing tumor growth.

Concluding remarks and learning objectives

Low dose CT is an effective technique for diagnosing asymptomatic stage IA non small cell lung cancer.

Effect on mortality from lung cancer is not known.

Cost per year of life saved has yet be determined.

Calculating cost and effectiveness will require a randomized trial or same equivalent.

Suggested reading

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