Screening for Lung Cancer*

The Guidelines

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Although virtually all individuals with advanced lung cancer succumb to the disease, a substantial portion of individuals diagnosed at an earlier stage can be cured. This dichotomy has provoked interest in lung cancer screening. To date, randomized controlled trials of chest x-ray and sputum cytology have failed to demonstrate that screening with either modality decreases lung cancer mortality; neither of these technologies can be recommended. Early studies of lung cancer screening with low-dose CT (LDCT) appear promising; however, only data from observational studies are available. We recommend that individuals should only be screened with LDCT in the context of well-designed clinical trials. (CHEST 2003; 123:83S–88S)

Key words: evidence-based medicine; lung neoplasms; mass chest x-ray; mass screening; practice guideline; sputum; tomography, x-ray computed

Abbreviations: CXR = chest x-ray; LDCT = low-dose CT; NCI = National Cancer Institute; PLCO = Prostate, Lung, Colorectal and Ovarian; RCT = randomized controlled trial

Lung cancer is the number-one cancer killer in the United States for both men and women, expected to claim the life of roughly 150,000 people in 2002. At present, the only therapy that achieves a high rate of cure is surgical resection of early stage disease. Hence, screening programs that can increase the rate of detection of early stage lung cancer make intuitive sense, and have been the subject of considerable enthusiasm for more than 50 years.

The recommendations we make regarding different screening approaches are based on a consideration of the evidence that is reviewed in this article and the accompanying evidence review. Our recommendations are broadly consistent with those produced by other organizations when evaluating the available early detection methods. These other guidelines are reviewed in Table 1.

Readers should appreciate that for some of these topics, the evidence is sparse and changing. As new data become available, these recommendations may change. The election to screen an individual at risk for lung cancer should be based on shared, informed decision making between provider and patient. These guidelines should complement that process.

CXR

Background

The rationale for CXR screening is based on the observation that most patients who are diagnosed with lung cancer have advanced stage disease that causes them to have symptoms. In contrast, CXR has sufficient resolution to detect small asymptomatic nodules that are often stage I disease. As stage I lung cancer can be treated through surgery, the efficacy of CXR would be mediated through the detection of lung cancer at an earlier stage, followed by a curative intervention such as removal of the cancer-containing lobe of the lung.

Prior Studies

Three randomized controlled trials (RCTs), one conducted in London in the 1960s, one conducted at the Mayo Clinic in Rochester, MN, in the 1970s, and one conducted in Czechoslovakia in the 1970s, each evaluated the impact on lung cancer mortality of regular CXR compared to less frequent CXR.8–10 The two latter studies also collected sputum cytology in conjunction with the CXR but the great majority
of incident lung cancers were independently detected by CXR. In all of these studies, more lung cancers were detected in the screened group than in the control group, but there was no discernible difference in cumulative lung cancer mortality. A provocative finding in all three studies was that the
excess cases of lung cancer seen in the screened group appeared to reflect an increased number of individuals detected with early stage disease, yet there were no discernible differences in the number with advanced stage disease.

**Ongoing Studies**

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial began recruitment for its main phase in 1994. The PLCO trial is an RCT in which 74,000 individuals aged 55 to 74 years will be screened for prostate, lung, colorectal, and ovarian cancers and followed up for at least 13 years from randomization. An additional 74,000 individuals will serve as control subjects receiving routine medical care. For the lung cancer-screening portion of the study, smokers will undergo a baseline posteroanterior CXR at entry and annual CXR for 3 years, whereas nonsmokers will undergo only two annual repeat screenings. The PLCO trial has an 89% power to detect a 10% reduction in lung cancer mortality.

**Recommendation**

1. For individuals without symptoms or a history of cancer, we recommend against the use of serial CXRs to screen for the presence of lung cancer. Level of evidence, good; benefit, none or negative; grade of recommendation, D

**Remarks**

Of the three RCTs of CXR screening, none demonstrated a mortality benefit. Despite the limitations of these studies, including relatively substantial crossover and contamination, it is incorrect to conclude that these methodologic problems negate the findings of these studies. In all three RCTs of CXR, there were clear and consistent differences in the rates and the stage distribution of lung cancer detection between the frequently screened and less frequently screened groups, substantiating the claim that the results of these studies do in fact reflect the impact of an active intervention. Therefore, although these studies provide incomplete knowledge about CXR, they are informative. None of these studies directly address the utility of a one-time “baseline” CXR in high-risk patients, which has perceived but undocumented value. Further information on the utility of serial CXR screening is anticipated after the completion of the PLCO trial.

**Studies of Sputum Cytology**

**Background**

The rationale for sputum cytology is based on the observation that many individuals have cancerous cells in their sputum at the time of lung cancer diagnosis. Sputum cytology is more sensitive for detecting squamous cell carcinomas, which tend to occur proximally in the bronchial tree, than for adenocarcinomas, which tend to arise more peripherally. Hence, the recent shift in histologic cell type from predominantly squamous to predominantly adenocarcinoma, noted in epidemiologic studies, may lessen the value of sputum cytology as a screening tool.

**Prior Studies**

Two randomized trials designed to examine the impact of sputum cytology supplementing CXR were conducted in the 1970s and 1980s. In these studies, conducted at Johns Hopkins and Memorial Sloan-Kettering Cancer Center, individuals were randomized to regular CXR with or without sputum cytology at 4-month intervals for at least 5 years. In neither of these studies was there a difference between the two study arms in the number of lung cancer cases detected, the percentage that was resectable, or the lung cancer mortality rates. Since the intervention (sputum cytology) failed to detect an appreciable number of new cancers not seen on CXR, the lack of any mortality benefit might be due to the insensitivity of the detection method that was used at the time.

**Ongoing Studies**

Improvements in detection of shed cancer cells in sputum samples has been proposed using multiple techniques, including immunohistochemical detection of aberrant proteins, computer-assisted image analysis, detection of genetic alterations, and detection of epigenetic alterations. These enhanced techniques are currently under study.

**Recommendation**

2. For individuals without either symptoms or a history of cancer, we recommend against the use of single or serial sputum cytologic evaluation to screen for the presence of lung cancer. Level of evidence, fair; benefit, none or negative; grade of recommendation, D

**Remarks**

At present, there is good evidence from RCTs that screening with sputum cytology does not appreciably affect lung cancer detection rates or lung cancer mortality, although in no case has sputum cytology been tested in individuals not being actively screened with CXR. Newer technologies for the
analysis of sputum may markedly improve the sensitivity of this test, which could lead to an alternative recommendation.

**LDCT Scanning**

**Background**

LDCT scanning is a technique that allows a low-resolution image of the entire thorax to be obtained in a single breath-hold with low radiation exposure. The test is very sensitive, and is capable of routinely detecting nodules as small as 2 to 3 mm in their greatest diameter. In addition, data obtained through LDCT and standard CT scans can be used to reconstruct three-dimensional images that can be assessed sequentially for evidence of growth. The rationale for LDCT as an improved early detection technology is therefore based on this twofold enhancement: the ability to detect very small nodules, and the ability to assess shape and growth patterns prior to invasive diagnostic tests. The expectation is that these enhancements will increase the proportion of individuals who receive diagnoses at an earlier stage, while also minimizing the number of individuals who undergo unnecessary procedures after an abnormality is first observed.

**Prior Studies**

LDCT is a relatively new technology that has only recently been studied in observational studies. Therefore, the evidence regarding LDCT is subject to the biases particular to this type of study. Currently available studies of LDCT demonstrate four phenomena. First, for individuals screened with LDCT and CXR, LDCT detects a far greater number of lung cancers than does CXR. Second, the vast majority of lung cancers detected by LDCT are stage I. Third, LDCT detects many more noncancerous than cancerous nodules. Fourth, the use of serial CT scans and three-dimensional reconstruction appears to lessen the number of invasive procedures performed on individuals who have an abnormality, but do not have lung cancer. No study has reported on survival outcomes for individuals who have screen-detected cancer. These observational data, coupled with concerns about overdiagnosis and inefficacy of treatment for screen detected disease, limit our ability to determine the potential efficacy of the intervention.

**Ongoing Studies**

At present, large observational and randomized studies of LDCT are either planned or underway. A large, New York-based LDCT study has begun, and is funded to enroll 10,000 current or former smokers for annual screening. The study should yield useful information on the frequency of abnormal test results, the diagnostic workup of patients with abnormalities, and the frequency of “unnecessary procedures” and interval-diagnosed cancers. In addition, after six PLCO sites successfully randomized > 3,000 individuals to LDCT or CXR screening in 2 months (the “Lung Screening Study”), the National Cancer Institute (NCI) approved a $200 million dollar study in which 50,000 individuals with a smoking history will be randomized to annual screening with LDCT or CXR at approximately 10 PLCO sites and approximately 20 American College of Radiology Imaging Network sites. This study is expensive and could take many years to complete, but it should yield useful answers. It is designed to have a 90% power to detect a mortality reduction of 20% and should be completed in 2009.

**Recommendation**

3. For individuals without symptoms or a history of cancer, we recommend against the use of a single LDCT or serial LDCTs to screen for the presence of lung cancer. At-risk individuals who express an interest in undergoing LDCT screening should be made aware of several ongoing high-quality clinical studies of this technology. Level of evidence, poor; benefit, none or negative; grade of recommendation, I

**Remarks**

Although studies of LDCT based on observational designs appear promising, in that LDCT detects a preponderance of early stage lesions, a similar pattern accompanied the early studies of CXR and sputum cytology. The fact that prior randomized studies of CXR and sputum cytology, related autopsy series, and preliminary findings in LDCT studies all raise concerns that some cancers detected by LDCT are overdiagnosed elevates the importance of proper evaluation of the technology. In addition, concerns about false-positive results and unnecessary treatment raise the possibility that even if LDCT leads to an improvement in lung cancer mortality through early detection, the test may in aggregate lead to greater harm than benefit.

As such, LDCT should be considered an experimental procedure that requires evaluation in the context of well-designed studies. Recently, the NCI approved the funding of a randomized study of LDCT that will accrue patients at approximately 10 of the NCI PLCO sites and approximately 20 sites designated by the American College of Radiology Imaging Network.
Imaging Network. In addition, numerous observational studies are underway. The NCI study is designed to estimate the efficacy of the test in lowering lung cancer mortality. Ongoing observational studies may provide supplemental insights about LDCT in terms of costs, frequency of follow-up tests, and rates of complications, but it is unlikely that they will in isolation answer the paramount question of efficacy. Whether randomized or uncontrolled:

1. Studies should be designed to evaluate high-risk subjects only, such as individuals ≥ 60 years old with at least a 30 pack-year smoking history. If individuals have quit smoking, it should have occurred no more than 10 years prior to enrollment. Studies that enroll low-risk subjects are unlikely to provide useful information about efficacy, and may cause harm during follow-up of findings.

2. Screening of subjects should be conducted at regular intervals (such as annually). Without longitudinal screening and extended follow-up, judgments about overdiagnosis and health-care events cannot be made. As a corollary, specific efforts should be made in the event of loss to follow-up.

3. It is vital that all study subjects maintain a record of health-care events occurring after screening visits. Of particular interest are interval-diagnosed cases of lung cancer and health-care encounters spurred by findings at LDCT. Without this information, neither the extent to which LDCT misses highly aggressive lung cancers, nor the cost and burden of positive findings can be assessed.

CONCLUSION

The most effective treatment for lung cancer remains surgical resection of early stage disease; however, sporadic lung cancer is rarely diagnosed in its earliest stages. The promise of screening techniques for increasing rates of early stage lung cancer detection, and thus the expectation of more treatable cases, has driven considerable research and ongoing development of screening technologies. RCTs of CXR and sputum cytology have failed to demonstrate a mortality benefit for either technique, and we do not recommend screening with serial CXR or sputum cytology for asymptomatic individuals or individuals without a history of cancer. LDCT scanning is a promising technology due to its sensitivity and ability to assess growth of nodules, and ongoing studies may provide additional information about the costs and benefits of screening with this technology. However, due to the absence of evidence regarding mortality and concerns about overdiagnosis, we recommend against screening with LDCT for individuals without symptoms or a history of cancer. As further research enhances our understanding of the risks and benefits, these recommendations may change.

RECOMMENDATIONS

1. For individuals without symptoms or a history of cancer, we recommend against the use of serial CXRs to screen for the presence of lung cancer. Level of evidence, good; benefit, none or negative; grade of recommendation, D

2. For individuals without either symptoms or a history of cancer, we recommend against the use of single or serial sputum cytologic evaluation to screen for the presence of lung cancer. Level of evidence, fair; benefit, none or negative; grade of recommendation, D

3. For individuals without symptoms or a history of cancer, we recommend against the use of a single LDCT or serial LDCTs to screen for the presence of lung cancer. At-risk individuals who express an interest in undergoing LDCT screening should be made aware of several ongoing high quality clinical studies of this technology. Level of evidence, poor; benefit, none or negative; grade of recommendation, I

REFERENCES


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