Original Article

Lung Cancer Screening

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Key Words

Lung cancer screening, low-dose computed tomography, observational studies, randomized controlled trials, chest radiograph, sputum cytology

Abstract

Because lung cancer frequently presents in an advanced stage when it is incurable, there has been a sustained search for an early diagnosis approach that could detect lung cancer when curable, while having few secondary consequences. Decades of research have evaluated various approaches to lung screening, including routine chest radiograph, sputum cytology, and, most recently, computed tomography (CT) scanning. No study has suggested that any of these approaches will identify life-threatening lung cancers at an earlier disease stage and allow alteration of their natural history. Therefore, no recommending body or professional society recommends using any of these approaches to screen for lung cancer. This general recommendation could change if randomized trials examining CT screening suggest that its benefits outweigh its harms. (*JNCCN* 2008;6:271–275)

Definition of a Beneficial Screening Test

For a lung cancer screening test to be beneficial, it must not only be able to detect early cancers but also alter the natural history of the specific lung cancers that would otherwise progress to cause disease, disability, or death. A beneficial lung cancer screening test would therefore reduce the likelihood that screened individuals would die of lung cancer. Therefore, the standard for evaluating lung cancer screening tests is to determine whether the test lowers lung cancer mortality rates in screened populations.[1] Surrogates of benefit, such as the frequency that early cancers can be detected through screening or the outcomes of individuals with screen-detected cancers, do not necessarily translate into actual benefits, as can be seen throughout the history of lung cancer screening research.

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Chest Radiograph Screening

Randomized studies conducted between 1950 and 1980 using chest radiograph (CXR) screening conducted in England, the United States, and Czechoslovakia showed that CXR screening is successful at uncovering early-stage cancers that would not otherwise have appeared (Table 1). Specifically, these studies found that individuals who were intensively screened had more early lung cancers discovered than those who were either less intensively screened or not at all.[2,7–9] The studies in the United States and Czechoslovakia also showed that the survival of individuals who had screen-detected early cancers was prolonged compared with those who had sporadically detected lung cancer.

However, neither of these seemingly favorable findings proved that CXR screening was beneficial. Instead, the studies showed that detection of early cancers did not prevent advanced cancers, because individuals in the screened groups developed advanced lung cancer as frequently as controls. Similarly for the finding of prolonged survival, what might have been a surrogate for improved outcomes was not. The number of individuals who died of lung cancer, or the rate at which they died, was similar across groups. This latter finding has now persisted in analyses stretching over 15 to 20 years of follow-up in some cases.[6,10]

Therefore, studies showed that CXR was not a beneficial screening test because it did not reduce the frequency of lung cancer death among screened subjects. This was true even though CXR clearly detected many early lung cancers, and survival after patients were diagnosed with early screen-detected cancer was prolonged.[11]

Table 1 Randomized Controlled Trials of CXR[2–6]

Study Site	Sample Size	Study Arms	Number of Lung Cancers Found During Study	Characteristics of Lung Cancers Found During Study		Deaths From Lung Cancer Over Period of Follow-up	
				Early-Stage	Late-Stage	No. of Deaths	Lung Cancer Mortality Rate (Per 1000 Person-Years)
London	29,723	CXR every 6 mo for 3 y	132	44	57	62	NR
	25,311	Single CXR at end of 3 y	97	22	54	59	NR
Mayo	4618	CXR and sputum cytology every 4 mo for 6 y	206	99	107	122	3.2
	4593	Advised to have CXR and sputum cytology annually	160	51	109	115	3.0
Czechoslovakia	3172	CXR annually	39	20	19	247	NR
	3174	CXR and sputum cytology at end of 3 y	27	10	17	216	NR

Abbreviations: CXR, chest radiography; NR, not reported.

CT Screening

First Findings

Interest in lung cancer screening was renewed in the late 1990s, based on studies of CT scanning conducted in Japan. Sone et al.[12] showed that CT scans performed on asymptomatic subjects showed more abnormalities than CXR, and some could be shown to be histologic foci of lung cancer. Numerous studies followed in Italy, Germany, and the United States, all showing the same general findings.[13–16] Namely, CT screening found many early lung cancers, more than appear sporadically in clinical practice, where most lung cancers are advanced.

The most recent study assessing detection rates came from Gohagan et al.,[17] who reported findings from screening subjects in the Lung Screening Study of the National Cancer Institute. CT screening identified more lung cancers than CXR, and a higher proportion of stage 1 lung cancers (48%) than CXR (40%). A few years after the initial reports in Japan, Sobue et al.[18] showed that survival of individuals with screen-detected lung cancer is prolonged relative to what is expected. Other investigators also reported this finding.[19,20]

As promising as these findings are, they are reminiscent of those from studies of CXR screening: CT screening uncovers more early cancers. In addition, survival for individuals with screen-detected lung cancer is longer than for those with clinically diagnosed lung cancer. Furthermore, the possibility exists that these putative surrogates of screening's efficacy would not actually indicate benefits for screened subjects. Addressing the link between these surrogate end points and patient outcomes characterized the next wave of research.

Later Findings

Determining whether these optimistic findings on CT screening indicate a benefit for patients has involved addressing the same 2 questions that were considered when evaluating CXR screening. First, does enhanced survival of individuals diagnosed through screening equate to a reduction in disease-specific mortality among screened subjects? Second, does finding more early cancers mean that the number of advanced cancers will be reduced?

The impact of CT screening on lung cancer mortality is currently being addressed in several large multicenter, randomized clinical trials. The National Lung

Screening Trial in the United States, which is the follow-on study to the Lung Screening Study, enrolled 50,000 subjects randomized to undergo CT or CXR screening; 3 rounds of annual screening currently have been completed. Follow-up is planned over the next several years, as are interim analyses. The study is powered to detect a 20% reduction in disease-specific mortality by the end of follow-up, but larger reductions would be apparent sooner (http://www.cancer.gov/nlst). Results will be available from this study by 2009 at the earliest. Randomized studies in Europe have also begun, including the Dutch–Belgian NELSON trial comparing CT screening with usual care, and plans are underway to launch similar trials in Norway, Germany, and Italy, and perhaps other countries. A pilot study in France was also just completed.[21]

The impact of CT screening on lung cancer mortality has been addressed using nonrandomized approaches, which have all concluded that CT screening does not reduce lung cancer mortality. Patz et al.[22] evaluated the reported characteristics of individuals screened in 1 large U.S. study and extrapolated the expected lung cancer mortality rates. In assuming that survival according to stage would mirror observed survival in population-based cancer registries, the investigators found that lung cancer mortality rates would likely not be reduced among subjects undergoing screening when comparing the expected mortality rates with those observed in other similar cohorts. In a study of 1520 smokers and former smokers who underwent 5 years of annual low-dose CT scans at the Mayo Clinic, Swensen et al.[23] found that lung cancer incidence and mortality rates were comparable to those in the study of CXR screening conducted in the 1970s and 1980s at the Mayo Clinic after adjusting subsets by age and sex.

Bach et al.[24] used prediction models to determine expected lung cancer mortality rates among 3 cohorts enrolled in screening programs in Italy and the United States, including the cohort analyzed by Swensen et al.[23] The prediction model for estimating expected lung cancer mortality rates was developed on a large cohort of subjects enrolled in a cancer prevention study, and shown to predict lung cancer death rates in 4 other cohorts within 5% to 10% of what had been observed, with no statistical evidence that the model either over- or underpredicted the observed event rates.[24,25] Among the 99% of subjects available for follow-up, Bach et al.[20] found no evidence that CT screening reduced lung cancer mortality through a median of 4.7 and a maximum of 6 years of follow-up. Between years 1 and 6, 38 deaths from lung cancer occurred among the 3 cohorts and 38.8 were expected ($P = .90$).

Bach et al.[20] also addressed the second question the CXR studies highlighted: does finding early cancers prevent advanced cancers? The study found that, despite CT screening uncovering many more early cancers than were expected, no evidence showed that the number of new diagnoses of advanced cancers was being reduced. In fact, the number of individuals diagnosed with advanced lung cancer during the study period was marginally higher than expected, with 42 cases of advanced lung cancer occurring, compared with 33.4 expected ($P = .14$).

Concerns About Harms

Other potential concerns have also been raised about CT screening. Bach et al.[20] found evidence that CT screening detects far more cancers than would be expected to occur sporadically, raising the specter that many lung cancers may be overdiagnosed, and thus clinically unimportant. In that analysis, found 3.2 times more cancers than expected and, because many of the additional lung cancers were early-stage, prompted 10 times more surgical resections than would have occurred in the absence of screening. These additional procedures, particularly those performed to resect indolent disease, are potentially a source of significant harm.

Other experts have raised concerns about the large number of abnormalities found with CT screening that are not histologic foci of lung cancer but still cause anxiety among patients, lead to repeat imaging, and sometimes prompt biopsies and lung resections. Swensen et al.[13] and Gohagan et al.[17] determined that patients screened for lung cancer had roughly a 50% chance of having some abnormality found after 1 or 2 rounds of screening. The impact of false-positives on patient well-being overall is difficult to quantify, but it is reasonable to assume that most patients experience anxiety and concern when found to have abnormalities on CT.

Concerns about radiation exposure from annual screening are also intermittently raised. Examining cardiac CT, Einstein et al.[26] estimated that cancer incidence could be measurably increased through routine scanning. In a modeled assessment of CT screening in patients with cystic fibrosis, de Jong et al.[27] estimated that a measurable increased risk for cancer was associated with routine CT use, which translated into some reduction in survival. For instance, in

Table 2 Recommendations Regarding CT Screening for Lung Cancer

Recommending Body	Topic	Recommendation
National Cancer Institute (http://www.cancer.gov/cancertopics/pdq/screening/lung/healthprofessional)	LDCT	The evidence is inadequate to determine whether screening reduces mortality from lung cancer. Based on solid evidence, screening would lead to false-positive tests and unnecessary invasive diagnostic procedures and treatments.
American Cancer Society (ACS)[28]	All modalities	Currently, neither the ACS nor any other medical/scientific organization, recommends testing for early lung cancer detection in asymptomatic individuals.
United States Preventive Services Task Force (http://www.ahrq.gov/clinic/uspstf/uspslung.htm)	CXR and sputum cytology and LDCT	Evidence is insufficient to recommend for or against screening asymptomatic persons for lung cancer with either LDCT, CXR, sputum cytology, or a combination of these tests.
Canadian Coordination Office for Health Technology Assessment (http://www.cadth.ca/media/pdf/213_ct_cetap_e.pdf)	LDCT	Currently, evidence does not exist to suggest that detecting early-stage lung cancer reduces mortality, and therefore screening with multislice/helical CT would be premature.
Society of Thoracic Radiology[29]	LDCT	Mass screening for lung cancer is not currently advocated. Suitable subjects who wish to participate should be encouraged to do so in controlled trials so that the value of CT screening can be ascertained as soon as possible.
American College of Chest Physicians[30]	LDCT	Do not recommend that LDCT be used to screen for lung cancer except in the context of a well-designed clinical trial.
National Comprehensive Cancer Network (www.nccn.org)	LDCT	The NCCN panel does not recommend the routine use of screening CT.

Abbreviations: CT, computed tomography; CXR, chest radiograph; LDCT, low-dose computed tomography.
Adapted from Bach PB, Silvestri GA, Hanger M, Jett JR. Screening for lung cancer: ACCP evidence-based clinical practice guidelines. 2nd ed. Chest 2007;132(3 Suppl):69S–77S.

men screened annually from age 2 who had an expected median survival of 26 years, life expectancy was shortened by a little more than 1 month because of CT radiation, whereas the risk for cancer death increased by a few percentage points. The risks that older individuals experience from annual CT screening for lung cancer cannot be perfectly extrapolated from these studies. However, the possibility that radiation could induce the development of lung cancer or other malignancies cannot be considered trivial when recognizing that the population eligible for screening would number in the tens of millions.

Clinical Practice Guidelines

Given that no randomized trial of CT screening has been completed, the suggestion from 3 analyses of single-arm studies using synthetic comparators that CT screening may not reduce lung cancer mortality, and emerging evidence of possible harms from CT scanning because of false-positives, overdiagnosis, and radiation exposure, no major professional organization or guideline development panel recommends lung cancer screening with CT (Table 2). Minor technical differences exist between the practice guidelines within the context of the "no" recommendation. The National Cancer Institute and United States Preventive Services Task Force emphasize the documented possibility of harms in the absence of any evidence of benefit in making its recommendation. The American Cancer Society notes the lack of evidence of benefit and the importance of relying on randomized trials for making public policy recommendations.[28] The American College of Chest Physician's guidelines emphasize the uncertainties regarding benefits and risks and the importance of clarifying these trade-offs in well-designed clinical trials with appropriate oversight but do not recommend any screening outside of trials.[30]

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