



TITLE: Low Dose Spiral Computerized Tomography (LDSC) Screening for Lung Cancer

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LOW DOSE SPIRAL COMPUTERIZED TOMOGRAPHY (LDCT) SCREENING FOR LUNG CANCER

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of low dose spiral computerized tomography (LDCT) as a modality for lung cancer screening. CTAF reviewed this topic in February 2007, and concluded that LDCT as a screening test for lung cancer did not meet CTAF criteria because it was not clear whether or not LDCT reduced lung cancer mortality. This topic is being addressed again because of the recent publication of the results of the National Lung Cancer Screening Trial, (NLST) which has been widely publicized and has renewed public interest in this topic.

BACKGROUND

In the United States in 2010, there were an estimated 222,520 new cases of lung cancer and 157,300 deaths from this disease.¹ The five year survival rate for this disease is only about 15%.^{2,3} Most lung cancers are not localized when first detected, but early detection is mandatory to improve prognosis. When stage I cancers are resected, five year survival ranges between 40%- 70%.³

In the 1970s, four large-scale randomized controlled trials (RCT), involving a total of 37,000 men (mostly smokers), were performed to determine the value of routine screening for lung cancer by chest x-rays and/or sputum cytology.⁴ Unfortunately, these studies provided strong evidence that screening does not lead to a decreased death rate from lung cancer. As a result of these trials, none of the major cancer guideline organizations (the American Cancer Society, the National Cancer Institute and the U.S. Preventive Services Task Force) recommend routine screening for lung cancer in asymptomatic individuals. However, because follow-up of at least one of these studies has shown improved survival for those patients who had their early stage lung cancer detected by chest X ray and sputum cytology and then resected surgically compared with those who received usual care⁵ and because of criticisms of the design of these studies, the National Institutes of Health (NIH) continues to investigate chest x-ray (CXR) for lung cancer screening as part of a large RCT: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial; the results of which are expected in 2015.^{9,10} In addition, since curable early cases of lung cancer are hard to visualize with conventional chest x-rays, investigators have turned to CT in the hopes of finding more cases at an early, resectable stage.^{2,3,11}

Low Dose Spiral (Helical) CT Scanning

In general, conventional chest CT is more sensitive for the detection of lung nodules (including cancers) than plain chest x-ray or whole lung tomography.^{12,13} Conventional CT has not been used to screen for lung cancer, however, because of the x-ray exposure dose, the time-consuming interpretation necessary, the large number of false-positive scans and the lack of proven cost-benefit.¹³ Because of its ability to continuously acquire data, the use of LDCT results in a shorter scanning time and a lower radiation exposure dose. LDCT uses multiple detectors and allows for high resolution volumetric imaging in a single breath hold. Use of a spiral CT scanning performed at 120 kVp, tube current of 50 mA, 1 sec/rotation, 10 mm collimation, and a pitch of 2.0 (table speed of 10 mm/sec) permits the entire lung to be scanned with ease during a single breath-hold in virtually all patients.¹⁴ The LDCT used for screening requires less than 20 seconds of scanning time and does not require intravenous contrast injection.¹⁵ The radiation dose is approximately 1.5 mSv, in contrast to the average effective dose with diagnostic chest CT of approximately 8 mSv¹⁶⁻¹⁹.

LDCT has been found by one group of investigators to be useful as a second step in patients screened for lung cancer with plain chest x-ray, particularly in finding small, early stage, peripheral lesions.²⁰ In addition, Itoh et al (1998) reported a comparison of LDCT to conventional CT of the lung in ten healthy volunteers and in 110 patients. Conventional CT detected a total of 196 lesions in the 110 patients. LDCT detected 177 (90%) of the 196 nodules (87 [96%] of 91 lesions greater than 5 mm in diameter), 54 of 57 focal parenchymal opacities, and 15 of 15 cases with fibrotic changes. Most of the lesions missed were less than 5 mm in diameter.¹⁴ LDCT does involve a greater radiation exposure dose to the patient than conventional chest x-ray, though it is less than 20% of the radiation exposure dose than conventional CT.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Spiral (helical) CT scanners are categorized as Class II devices by the FDA. There are many spiral (helical) CT scanner systems that have been approved by the FDA under the 510(k) approval process. CT scanners are labeled for general use on the whole body rather than for a specific body part. Examples of CT scanner systems approved



by the FDA include The ImageChecker (R2 Technology, Sunnvale, CA), The Syngo Lung Care CT (Siemens, Malvern, PA), and Hi Speed Advantage and Lightspeed QX/j (General Electric Medical Systems, Milwaukee, WI).

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words 'lung cancer', cross-referenced with the keywords 'screening' and 'CT'. The original search was performed for the period from 1966 through January 2007. We repeated the literature search for the updated assessment for the period from January, 2007 through July, 2011. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

There have been nine peer-reviewed published studies of LDCT to screen for lung cancer to date. All nine of them have been with high risk or mixed risk screening populations. The earliest study was cross-sectional¹³; six of the subsequent seven were longitudinal cohort studies,²¹⁻²⁶ one was a randomized controlled trial (RCT) intended as a feasibility pilot study,²⁷ and the final study (the National Lung Screening Trial or NLST) was a randomized controlled trial that published data on mortality.¹⁶

No studies to date have evaluated the impact of screening for lung cancer with low dose CT on society as a whole. There is theoretic concern that the availability of screening might reduce concern about lung cancer and therefore undermine prevention efforts focused on discouraging smoking or encouraging smoking cessation. It is also possible that the resources drawn to screening and follow-up of abnormal results could adversely affect health of those not screened. To date, no studies have evaluated these issues.

Level of Evidence:1, 4, 5

TA Criterion 2 is met for the use of LDCT for screening high risk individuals.

TA Criterion 3: The technology must improve the net health outcomes.

Benefit

The design, outcomes, and results of the nine published trials are detailed in the Table below. As described above, the earliest study, by Kaneko et al, was cross-sectional, assessing lung cancers seen on LDCT and comparing that number to the number seen on CXR in the same patients.¹³ This design provides information about the prevalence of lung cancer seen by the two modalities, as well about the stage of those cancers diagnosed based on LDCT. Seven of the nine remaining studies were longitudinal cohort studies which did a baseline screening by LDCT and then follow-up screening, ranging from a single annual screen to screens every six months for five years.²¹⁻²⁶ This design allows for information about both the prevalence of lung cancer seen on LDCT and its ability to detect incident cancers over time. Three of these trials compared lung cancer detection rates on LDCT to that on CXR,^{24,25,16} one trial compared outcomes to historical controls from the Mayo Lung Project,²⁶ and three trials made no comparison at all.²¹⁻²³ The eighth study was an RCT which randomized participants to receive either a LDCT or a CXR to screen for lung cancer at baseline and at one subsequent annual visit.²⁸ Although quite large, this trial was intended to study the feasibility of randomizing to the two modalities, and to assess the number of participants required in each arm of a future, larger RCT (the NLST) examining this question in order to see a clinically significant difference between the two groups. The final study, the NLST¹⁶ was a large RCT with the goal of evaluating the impact of LDCT screening on lung cancer mortality.

Smoking is clearly the single most important risk-factor for lung cancer.^{2,3,29} Given that lung cancer is uncommon in non-smokers, trials of screening tests should focus on those at highest risk (e.g. those with a significant smoking history). Of the eight studies, four included only smokers or past-smokers^{13,21,26,27}; while the other four included a mixed-risk population, ranging from 46%-86% smokers.²²⁻²⁵ The studies with high-risk only populations found a prevalence of lung cancer on LDCT (baseline screen) of 1.2%-2%, and an incidence of lung cancer on LDCT (follow-up/annual screens) of 0.6%-2%. The studies with mixed-risk populations found a prevalence of lung cancer on LDCT of 0.42%-1.3%, and an incidence of lung cancer on LDCT of 0.1%-0.6%. The majority of lung cancers found on LDCT in all studies were Stage I, ranging from 53%-93% at the baseline screen.

Five of the studies reported on mortality. Sone et al reported lung cancer specific mortality after variable, relative short-term follow-up of 1.2-3.7 years. With only 60 cases of whom 2 died, lung cancer mortality in this study was 3.3%²⁵ Sobue et al reported lung cancer specific five year mortality of 15% for their 36 cases.²⁴ Diedrich et al reported lung cancer specific mortality after variable follow-up of two to 40 months of 27% for their 11 cases.²¹ Swenson et al reported a mortality rate of 2.8 per 1000 years and compared it to the overall mortality in the Mayo Lung Project (intensively screened and less intensively screened) of 2.0 per 1000 years, demonstrating a difference

that was not statistically significant (2.8 vs 2.0: P=0.43).²⁶ Henschke et al reported an estimated ten year lung cancer specific mortality (after an average of five years follow-up) of 20% for their 484 cases; they also estimated the ten year lung cancer specific mortality for those participants with Stage I cancers found on LDCT at 12%.²²

The most recent observational study (Henschke et al), was a very large (n=31,567) international study which included mostly high risk smokers (83%), a smaller number of participants with second-hand smoke exposure (12%), and an even smaller number with occupational exposure to toxins such as asbestos (5%). Outside of an extensive protocol for follow-up of abnormal scans, which allowed the investigators to minimize unnecessary invasive procedures,^{15,30} and formal adjudication of all cases, the design of this study was not substantially different from previous studies. This was a large cohort study with a baseline screen by LDCT, and a follow-up “annual” screen for most participants, with no comparison group. Thus, the results of this study are subject to all of the same potential biases as those of preceding studies.

Several observational studies had shown that screening lung CT could detect more nodules and lung cancers than conventional chest x ray but could not determine the impact of LDCT on lung cancer mortality. The goal of the National Lung Screening Trial (NLST), a randomized trial of screening CXR compared with screening LDCT, was to determine the impact of screening CT on mortality reduction from lung cancer when compared with chest radiography. The NLST began in 2002 and the results were recently reported in 2010.

The NLST, which was conducted in 33 centers, randomized 53,454 high risk individuals to receive annual screenings with either LDCT or single view PA chest X ray. The main outcomes were lung cancer incidence and lung cancer mortality. Outcomes were measured through December 31, 2009. Eligible participants were aged 55-74 at the time of randomization and had to have smoked at least 30 pack years. If they were former smokers, they had to have quit within the previous 15 years. The results of any abnormalities found on screening CT were provided to the participant’s physician, who then determined the follow-up plan.

For low dose CT, a positive test was defined as any noncalcified nodule or mass that measured at least 4 mm in diameter. Other abnormalities, such as a pleural effusion or adenopathy were also classified as “positive.” After the third round of annual screening, abnormalities that had remained stable over the three rounds of screening were classified as minor abnormalities and not as “positive” results, given that more worrisome lesions would have been expect to change.

All CT scans were read and interpreted by highly trained and certified NLST radiologists. More lung cancers were detected in the LDCT group than in the radiography group (rate ratio 1.13:95% C.I.: 1.03-1.23). In addition, there were fewer deaths in the LDCT group (247 vs 309 deaths per 100,000 person-years) resulting in a 20% reduction in mortality from lung cancer in the low dose CT group (95% C.I. 6.8 to 26.7). All cause mortality was also reduced in the LDCT group compared with the radiography group (6.7% reduction: 95% C.I. 1.2 to 13.6). Overall, the number needed to screen annually for three years to prevent one lung cancer death was 320.

Potential Biases

The desire to find a screening test for lung cancer which will catch the disease at an early, resectable stage is soundly based in the principles of screening.³¹ Screening principles require that the disease for which we are screening be an important cause of morbidity or mortality, which lung cancer certainly is. It also requires, however, that the screening test leads to net benefit for the screened population (and perhaps for the population overall), and in the case of lung cancer this means decreasing cancer-specific mortality while not increasing mortality from the test or resultant interventions themselves. In the study by Swenson et al, LDCT did not reduce mortality compared to historical controls. None of the other studies compared mortality rates for screened versus control populations; they only reported on mortality rates for their screened populations. While the Henschke et al study is promising in that they showed an estimated ten year mortality rate for early stage cancers that was much lower than if those cancers were to go undetected and untreated, this was a subanalysis and there was no control group. It remains a concern with all of these studies that the detection of a high proportion of early stage lung cancers is a result of either lead-time or length-time bias.

Lead time bias is of particular concern in observational studies without a control group. In screening, lead-time is the time between when the diagnosis of a disease is made by the screening test and when the disease would have presented clinically. Lead-time bias occurs when survival is counted from the time of the diagnosis by the screening test, but is only measured in these cases. In other words, lead-time bias falsely increases survival time for those patients being screened by identifying the disease earlier than it would have otherwise been identified, but not increasing actual survival from the disease. Thus, even if the screening is ineffective in increasing survival, making an earlier diagnosis will add lead-time to the survival measured for those patients with disease. Lead-time bias can be avoided by measuring mortality (or survival) among all screened and control subjects, not just measuring the mortality rate from diagnosis for cases (those with disease).³²

Length time bias is also of potential concern with observational studies. Length-time bias occurs when the disease being detected by a screening test has a more indolent natural history than disease that goes undetected by the

screening test.³² In other words, in the case of LDCT screening for lung cancer, the majority of cancers detected have been small, peripheral disease. It is possible, that this presentation represents a more indolent variation of disease than cancers not detected by screening, and thus cases diagnosed by LDCT would have lower mortality to begin with. Over-diagnosis bias is also of concern; in this scenario, some of the “disease” being diagnosed by the test is not really disease at all. Again, the best way to avoid length-time and over-diagnosis biases is to randomize participants to screening and control groups, and then compare the mortality of all subjects– those in the screened group and those in the control group.³²

Individuals who volunteer to participate in a screening study may be inherently different (healthier) than those who do not. They may have healthier habits, better access to healthcare, and different education or income levels. All of these differences could lead to a better prognosis for those participants, making it appear - in a study without a similar comparison group - that it is the screening test leading to a better outcome, when really the better outcome is inherent to the patient population being studied.³²

Potential Harms

The observational studies which have included only high risk populations (current or former smokers), have found a high rate of non-calcified nodules >4mm on LDCT baseline screening, ranging from 10%-43%.^{13,21,26,27} Of these, up to 93% are false positive tests.²⁶ In the recent NLST randomized trial, at the baseline screen 27.3% of those in the LDCT group had a positive test, in contrast to only 9.2% in the radiography group. Overall, over the three rounds of screening, the rate of positive screening tests was 24.2% with LDCT and 6.9% with radiography over all three rounds. Among these positive tests, the vast majority were false positives. 96.4% of the positive LDCT results were false positives and 94.5% of those in the radiography group were false positives. The results of the LDCT and subsequent diagnostic follow-up are described in Table 2. Overall, 75,000 CT scans were performed leading to 18,146 positive tests. Of these, 17,055 were false positive tests. A total of 713 thoracotomies or mediastinoscopies, 671 bronchoscopies and 322 percutaneous cytology exams or needle biopsies were performed to prevent 62 deaths from lung cancer. The number needed to screen to prevent one death from lung cancer was 320.¹⁶

Table 1: Outcomes and Diagnostic Follow-up of Positive LDCT Screening Results in Three Rounds of Screening in the NLST

Number of LDCT Scans	75,126
Number of Positive Tests	18,146
Number of False Positive Tests	17,497 (96.4%)
Number requiring any diagnostic follow-up	12,757 (72.1%)
Number requiring percutaneous cytologic examination or biopsy	322 (1.8%)

Number requiring bronchoscopy	671 (3.8%)
Number requiring a surgical procedure	713 (4.0%)
Number of lung cancers found	649 (3.6%)

All of these nodules require follow-up, at a minimum by conventional CT, and at a maximum by surgical biopsy. Henschke et al have shown that it is possible to avoid much of the most invasive follow-up by following a complex, standardized protocol.²² However, none of this follow-up is completely without risk – surgery, of course, carries risks of bleeding, infection, and death, but even a follow-up conventional CT carries some risk of increased radiation exposure and increased anxiety.³³ The published literature to date has not adequately assessed these long-term risks.

In addition, the adverse effects of higher radiation exposure due to the LDCT itself, particularly if repeated at a regular interval are unknown.³⁴ One researcher estimates that if 50% of all current and former smokers in the U.S. age 50-75 years old underwent annual LDCT screening for lung cancer, the radiation exposure from the screening tests themselves would result in a 1.8% increase in lung cancer cases among those screened.³⁵ In the NLST, screening was performed annually for three years, however this screening interval has not been compared with any other interval of screening. It remains unclear from current studies how much benefit is really accrued by repeat annual screens, or if a longer screening interval would be equally or more beneficial.

Summary

The NLST has conclusively shown that screening LDCT can reduce lung cancer mortality and total mortality in a group of high risk individuals. This reduction in mortality was seen in the face of a very high incidence of false positive tests. Important questions remain. Will the mortality reduction be seen in other populations at differing lung cancer risk? If screening is effective, at what interval should screening be performed to maximize benefit? What is the appropriate follow-up for the nodules identified on LDCT screening? Several of the ongoing European studies are addressing these important questions of frequency of screening and appropriate follow up of screen detected nodules. Finally, with the increasing concern about radiation exposure and long term cancer risk, future studies must address and include this potential risk.³⁶ Thus at this point there are clear benefits in terms of mortality reduction to lung cancer screening of high risk individuals with LDCT, it is not yet known whether or not the benefits outweigh the risks in the overall population.

TA Criterion 3 is met for high risk individuals similar to those enrolled in the NLST.

Table 2. Design and Results of English Language Published Studies of LDCT for Lung Cancer Screening

Study	Population	Design	Comparison	Outcome	Results
Kaneko et al 1996 ¹³	1,369 high risk screening population 90% male Age 38-83 All smokers	Cross-sectional Combined data for baseline screen and up to 3 additional bi-annual screen	CXR – same participants	Positive exam Lung cancer diagnosis Detection on CXR Stage	588 positive CT 15 (0.43%) lung cancer cases 11 (73%) not visible on CXR 14/15 (93%) Stage I
Sone et al 1998, 2001 ^{25,37}	5,483 screening population 54% male age 40-74 46% smokers	Longitudinal Baseline screen Annual screen x 2 subsequent years	CXR – same participants	Suspicious nodule Lung cancer diagnosis Detection on CXR Stage Mortality at follow-up	<u>Baseline screen (n= 5,483)</u> 279 (5.1%) suspicious nodules; 23 cancers (0.42%) <u>Year 1 annual screen (n=4,425)</u> 178 (3.9%) suspicious nodules; 27 cancers (0.61%) <u>Year 2 annual screen (n=3,878)</u> 136 (3.5%) suspicious nodules; 10 cancers (0.26%) 67% not visible on CXR (retrospectively) 53/60 (88%) cases Stage I <u>1.2-3.7 years f/u:</u> All cause mortality 5/60 = 8.3% Lung cancer mortality 2/60 = 3.3%



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Study	Population	Design	Comparison	Outcome	Results
Sabue et al 2002²⁴	1,611 screening population 88% male age 40-79 86% smokers	Longitudinal Every 6 month screening for up to 5 years (all underwent at least 2 screens)	CXR; Sputum cytology – same participants	Positive test Lung cancer diagnosis Stage 5-year mortality	<p><u>Baseline screen (n=1,611)</u> 186 positive CT 77% not visible on CXR 96% not detected on sputum cytology</p> <p>14 lung cancer cases (0.87%) 1 case found only on sputum cytology Total cases found on CT: 13 (0.81%) 10/13 (77%) Stage I</p> <p><u>Repeat screens (n=7,891 over 5 yrs)</u> 721 positive CT 88% not visible on CXR 99% not detected on sputum cytology</p> <p>22 lung cancer cases (0.28%) 3 cases found only on sputum cytology Total cases found on CT: 19 (0.24%) 15/19 (79%) Stage I</p> <p><u>5-year mortality for all cases (n=36)</u> All cause mortality = 29% Lung cancer mortality = 15%</p>



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Study	Population	Design	Comparison	Outcome	Results
					Diagnosed at baseline screen = 24% Diagnosed at repeat screen = 30%
Nawa et al 2002²³	7,956 screening population 79% male age 40-69 77% smokers	Longitudinal Baseline screen Annual screen x 1 subsequent year	No comparison	Positive test = non-calcified pulmonary nodule ≥ 8mm Lung cancer diagnosis Stage	<u>Baseline Screen (n=7,956)</u> 541 positive tests requiring detailed CT 64 required invasive follow-up 36 (0.45%) cases of lung cancer 31/36 (85%) Stage I <u>Annual Screen (n=5,568)</u> 148 positive tests requiring detailed CT 7 required invasive follow-up 4 (.07%) cases of lung cancer 4/4 (100%) Stage I
Diedrich et al 2002²¹	817 high risk screening population 72% male Age 40-79 All smokers; 45 pack year median hx (range 20-166)	Longitudinal Baseline screen Follow-up screening x 2 years for patients with morphologically benign nodules found at baseline	No comparison	Initial positive test = non-calcified pulmonary nodule Follow-up positive test = ≥ 10 mm and read as likely malignant on follow-up thin-section low dose CT Lung cancer	<u>Baseline Screen (n=817)</u> 350 initial positive test 29 follow-up positive test 12 underwent biopsy immediately 10 (1.2%) cases of lung cancer (with 12 tumors) 7/12 (58%) Stage I <u>2-year Follow-up Screen</u>



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Study	Population	Design	Comparison	Outcome	Results
				diagnosis Mortality	<p><u>(n=17)</u> 1 grew at 24 months, biopsied 1 case Stage I lung cancer</p> <p><u>2-40 months f/u:</u> All cause mortality 4/11 = 36% Lung cancer mortality 3/11 = 27%</p>
<p>Swensen et al 2002, 2003, 2005^{26,38,39}</p>	<p>1520 high risk screening population 52% male Age 50-85 All smokers ≥ 20 pack year history; 45 pack year median (range 20-230)</p>	<p>Longitudinal Baseline screen Annual screen x 4 subsequent years</p>	<p>Comparison to historical controls from Mayo Lung Project (MLP) – subset of men > 50 with 4 years of follow-up</p>	<p>Positive test = non-calcified pulmonary nodule False positive test rate Lung cancer diagnosis Stage Mortality</p>	<p><u>Baseline Screen (n= 1520)</u> 749 nodules any size 404 nodules > 4mm 96% false positive rate for nodule any size 93% false positive rate for nodule > 4mm 31 (2%) lung cancers 22 (76%) of non-small cell cancers Stage I</p> <p><u>Annual Screens (n=1490)</u> 773 nodules any size 378 nodules > 4mm 96% false positive rate for nodule any size 93% false positive rate for nodule > 4mm 32 (2%) lung cancers 17 (61%) of non-small cell cancers Stage I</p>



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Study	Population	Design	Comparison	Outcome	Results
					<p><u>Comparison to Mayo Lung Project</u> Mortality: CT screened 2.8 per 1000 person-years MLP overall 2.0 per 1000 person-years</p>
<p>Gohogan et al 2004, 2005^{27,28}</p>	<p>3,318 high risk screening population 59% male Age 55-74 All smokers ≥ 30 pack year history; 54 pack year median</p>	<p>RCT pilot feasibility study – randomized to CXR (1,658) versus LDCT (1,660) Baseline screen Annual screen x 1 subsequent year</p>	<p>CXR – randomized comparison group</p>	<p>Positive test = non-calcified pulmonary nodule ≥ 4mm or any other finding radiologist considered suspicious of malignancy Lung cancer diagnosis Stage Adherence to study protocol</p>	<p><u>Baseline Screen (n=3,318)</u> 325 positive LDCT 30 (1.9%) lung cancer cases 16 (53%) Stage I 152 positive CXR 7 (0.45%) lung cancer cases 6 (86%) Stage I <u>Annual Screen (n=2,656 negative at baseline)</u> 221 positive LDCT 8 (0.57) lung cancer cases 2 (25%) Stage I 93 positive CXR 9 (0.68) lung cancer cases 2 (22%) Stage I <u>Adherence to randomization & follow-up</u></p>



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Study	Population	Design	Comparison	Outcome	Results
					<p>LDCT screen completion: Baseline 96% Annual 86% Receipt of CXR after negative annual exam: 20%</p> <p>CXR screen completion: Baseline 93% Annual 80% Receipt of spiral CT after negative annual exam: 2.2%</p>
Henschke et al, 1999, 2001, 2006 ^{15,22,40}	31,567 mixed risk population ?% male Age 40-85 Mixed population 83% smokers 12% exposure to 2 nd hand smoke 5% occupational exposure Median 35 pack year history (range 0-141)	Longitudinal Baseline screen and annual screen x 1 subsequent year	No comparison	Positive test = at baseline solid pulmonary nodule ≥ 5mm or nonsolid nodule ≥ 8mm; at annual new non-calcified nodule Lung cancer diagnosis Stage Estimated 10-year mortality for stage I cancers	<p><u>Baseline Screen (n= 31,567)</u> 4,186 positive test 405 (1.3%) lung cancers</p> <p><u>Annual Screen (n=27,456)</u> 1,460 positive test 74 (0.27%) lung cancers</p> <p>5 cases interim diagnoses of lung cancer</p> <p>412/484 (85%) Stage I</p> <p>Estimated 10-year lung cancer specific mortality (average follow-up 5 years) All cancers 20% For Stage I cancers 12%</p>
NLST, 2011 ¹⁶	53,454 high risk (48% current smokers and 52%	RCT randomized to CXR (26,732) vs LDCT	CXR=randomized comparison group	Lung cancer mortality All cause mortality Follow up of positive	<p><u>Lung cancer mortality: 20% reduction in LDCT group</u> <u>All cause mortality: 6.7%</u></p>

Study	Population	Design	Comparison	Outcome	Results
	former smokers) 59% male	(26,722)		test results Adverse events Incidence and characteristics of lung cancers	reduction in LDCT group <u>False positive screens:</u> 24.2% with LDCT and 6.9% with CXR <u>Lung cancer incidence:</u> higher in LDCT group (rate ratio 1.13: 95% C.I. 1.03 to 1.23)

CXR Chest X ray
LDCT: Low Dose Computed Tomography
NLST: National Lung Screening Trial

TA Criterion 4: The technology must be as beneficial as any established alternatives.

There are no established alternatives for lung cancer screening. If the overall goal is to reduce lung cancer mortality, then efforts directed toward getting people to quit smoking or to not start smoking in the first place could be considered the established alternative. However, if the focus is on screening as a secondary prevention measure, then it is important to determine whether or not there is any appropriate alternative.

As noted above in the background section, past trials of sputum cytology and CXR have failed to show a mortality benefit. Because of criticisms of the design of the prior negative trials, particularly the lack of power to detect less than 50% reduction in lung cancer mortality, the NIH is currently sponsoring a large cancer screening RCT - the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial – which is examining the impact of CXR screening on lung cancer mortality.¹⁰ During the design phase of the NLST, the comparison group was carefully considered. Although CXR is not a currently established lung cancer screening modality, it is currently being evaluated as a screening test in the PLCO trial. If the results of the PLCO study reveal that it is an effective lung cancer screening modality, then it would be an important comparator to LDCT. Thus, the NLST was designed to compare LDCT to CXR, so that if CXR is eventually established as a lung cancer screening modality, the NLST would answer the question of whether LDCT is as or more beneficial than CXR.⁴¹

There are six ongoing RCTS evaluating LDCT in lung cancer screening in Europe (Table 3). Four of these are comparing LDCT with usual care⁴²⁻⁴⁵, and two are comparing LDCT with CXR.^{27,46,47} None of these studies is as large as the NLST and none are sufficiently powered to show a mortality reduction, although meta-analyses will probably be performed. In addition, these studies are collecting additional data that will inform other questions such as how to determine the best strategies for evaluating the lung nodules seen with CT screening.

The NLST has shown that LDCT screening for lung cancer results in a reduction in lung cancer mortality when compared with CXR screening in high risk individuals in specialized centers. This reduction in mortality occurs in the face of an extremely high rate of false positive results, many of which require additional testing and follow-up and some which require invasive procedures. Even if CXR becomes an established alternative for lung cancer screening, future studies must address the overall risks and benefits associated with each screening procedure.

TA Criterion 4 is met for high risk individuals at specialized centers.

Table 3: Baseline Characteristics of Ongoing RCTS of low dose CT lung cancer screening

Name	N	Intervention	Age	Sex	Smoking hx/Ex smokers Quit (yr)	Screening duration	Year final results expected
Garg et al 2002 ⁴²	92 LDCT 98 controls (190)	LDCT vs usual care	50-80	97.4% male and 2.6% female	.30 years	2001 (1 year)	Not applicable (feasibility study)
Lopes Pegna et al 2009 ⁴³	1613 LDCT 1593 controls (3206)	LDCT vs usual care	55-69	64.7% male and 35.3% female	>20/<10	2004-2006	2012
Gohagan et al 2004, 2005 ^{27,28} Clark et al 2009 ⁴⁶	1660 LDCT 1658 CXR (3318)	LDCT vs CXR	55-77	59% male and 41% female	>30/<10	2000-2004	2011 (NLST)
Blanchon et al 2007 ⁴⁷	385 LDCT 380 controls (765)	LDCT vs CXR	50-75	71% male and 29% female	>15/<15	2002-2004	n/a
Infante et al 2008 ⁴⁴	1276 LDCT 1196 controls (2472)	LDCT vs usual care	60-74	100% male	>20/<10	2001-2006	n/a
Pedersen et al 2009 ⁴⁵	2052 LDCT 2052 controls (4104)	LDCT vs usual care	49-74	55.2% male and 44.8% female	>20	2004-2006	2011

Table adapted in part from Gopal M, Abdullah SE, Grady JJ, Goodwin JS. Screening for lung cancer with low-dose computed tomography: a systematic review and meta-analysis of the baseline findings of randomized controlled trials. *J Thorac Oncol.* Aug 2010;5(8):1233-1239.⁴⁸

TA Criterion 5: The improvement must be attainable outside the investigational settings.

The multi-center NLST study was conducted at centers known for their expertise in radiology as well as cancer diagnosis and treatment, and the radiologists and radiology technologists were extensively trained, which may limit generalizability to screening performed in the community setting. On the other hand, follow-up of abnormal tests was conducted by participants' personal physicians, which is more similar to what happens in the community setting, thus



increasing generalizability. It is likely that with appropriate guidelines for reading the LDCT and appropriate follow-up guidelines, this will be attainable in the future outside specialized centers, although this has not yet been shown.³³

TA Criterion 5 is met for high risk individuals at specialized centers.

CONCLUSION

In summary, until the recent publication of the NLST, the majority of studies of LDCT for lung cancer screening were observational and were fraught with the inherent biases of observational studies. The recent publication of the NLST has conclusively shown that lung cancer mortality and total mortality can be reduced with LDCT screening of high risk individuals. However, although the important mortality question was answered, many other important other questions remain unanswered. First, and foremost, there is a very high rate of false positive tests. Many of these test results require additional evaluation and additional procedures, and potential risks and benefits of these additional evaluations are not known. In addition, even if screening is ultimately shown to be associated with a net benefit, important questions remain about whom to target for screening and also about the appropriate interval for screening. Finally, cumulative radiation exposure is associated an increased risk of radiation induced cancers, and the extent of this risk potentially attributable to LDCT is not currently known. Thus, use of LDCT screening cannot currently be recommended outside of the investigational setting. We await further analyses from the NLST as well as the results of some of the European studies and any subsequent guidelines on reading and follow-up of positive LDCT screening exams.

RECOMMENDATION

It is recommended that the use of LDCT as a screening test for lung cancer in high risk individuals at specialized centers meets CTAF criteria 1-5.

The California Technology Assessment Forum panel voted nine in favor of the recommendation and three opposed.

October 19, 2011

This is the second review of this topic by CTAF.



RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted a review of this technology.

Centers for Medicare and Medicaid Services (CMS)

There is not a National Coverage Determination specific to the use of this technology for lung cancer screening.

American Cancer Society (ACS)

ACS does not have a guideline on screening for lung cancer. The ACS website states that ACS is convening experts in lung cancer, cancer screening, health practices, and ethics to review the data from the NLST. The date of completion of the review was not available.

American Society of Radiation Oncology (ASTRO)

ASTRO has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

Society of Thoracic Radiology (STR)

STR is convening a task force to address this topic. It is expected that the STR task force will have a position statement on this technology in about a year. Until the completion of the task force analysis, STR states that they currently support the findings of the National Lung Screening Trial (NLST).

California Radiological Society (CRS)

The CRS has been invited to provide an opinion and to send a representative to participate at the meeting.

California Thoracic Society (CTS)

The CTS has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

Association of Northern California Oncologists (ANCO)

ANCO has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.



International Association for the Study of Lung Cancer (IASLC)

IASLC has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

Medical Oncology Association of Southern California (MOASC)

MOASC has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

American College of Chest Physicians (ACCP)

The ACCP guidelines regarding Lung cancer are available at: http://www.chestjournal.org/content/vol123/1_suppl/.

U.S. Preventive Services Task Force

The US Preventive Services Task Force website

(<http://www.uspreventiveservicestaskforce.org/uspstf/topicsprog.htm>) indicates that lung cancer screening is one of the topics being reviewed. No further information was provided.



ABBREVIATIONS USED IN THIS ASSESSMENT:

LDCT: Low dose spiral computerized tomography

NLST: National Lung Screening Trial

NCI: National Cancer Institute

RCT: Randomized controlled trials

NIH: National Institutes of Health

CXR: Chest x-ray

PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

DARE: Database of Abstracts of Reviews of Effects

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