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The evidence for low-dose CT screening of lung cancer

Kathleen Ruchalski *, Antonio Gutierrez, Scott Genshaft, Fereidoun Abtin, Robert Suh

David Geffen School of Medicine at UCLA, Department of Radiology, 757 Westwood Plaza, Ste 1621, Los Angeles, CA, 90095-1721

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ABSTRACT

Lung cancer remains the leading cause of cancer-related death in the United States. An effective screening tool for early lung cancer detection has long been sought. Early chest radiograph and low-dose computed tomography (LDCT) screening trials were promising and demonstrated increased cancer detection. However, these studies were not able to improve lung cancer mortality. The National Lung Screening Trial resulted in decreased lung cancer mortality with LDCT screening in a high-risk population. Similar trials are currently underway in Europe. With LDCT now being widely implemented, it is paramount for radiologists to understand the evidence for lung cancer screening.

1. Introduction

Lung cancer is the leading cause of cancer mortality and accounts for approximately 27% of all cancer-related deaths. While lung cancer is the third most common cancer diagnosed, it results in higher mortality rates than breast, prostate, and colon cancer combined [1]. Partly related to the advanced stage of disease at the time of diagnosis, nearly 90% of those diagnosed with lung cancer will die from their disease, with 1- and 5-year survival rates from 2003 to 2009 as low as 43% and 17%, respectively [1,2]. Ongoing advances in surgical techniques, chemotherapy, radiation therapy, and percutaneous ablation for lung cancer are promising; however, the long-term survival from lung cancer currently remains low [3].

Cigarette smoking is estimated to account for up to 90% of lung cancers [4], with the relative risk for lung cancer approximately 20-fold higher in smokers compared to nonsmokers [4,5]. A direct dose response relationship exists for the amount of daily use and years of smoking with risk of lung cancer. While smoking prevention and cessation programs play a significant role in decreasing smoking rates and lung cancer mortality, millions of current and former smokers remain at substantial risk for the disease [6,7].

Screening examinations aim to detect disease early in an asymptomatic at-risk population, with the goal of prolonging life and improving quality of life. To be effective, the screening program must balance the potential benefits and harmful effects to both the individual and population as a whole. Currently, only 15% of lung cancers are diagnosed at a localized state, with a 5-year morality of 54% compared to 17% for all stages [1]. Therefore, abundant effort has been made to develop an effective screening tool for lung cancer.

2. Screening

2.1. Chest radiography and sputum cytology

Early studies, dating back to the 1960s focused on the use of chest radiography and sputum cytology for the early detection of lung cancer. The Early Lung Cancer Cooperative Group, a multiinstitutional program of the National Cancer Institute, was formed in the late 1960s and resulted in several randomized controlled clinical trials evaluating the utility of chest radiographs and sputum cytology in lung cancer detection. Both the Johns Hopkins Study and Memorial Sloan–Kettering Study investigated the outcomes of combined sputum cytology and screening chest radiograph without improved lung cancer mortality with screening [8,9].

The Mayo study, also a subset of the Early Lung Cancer Cooperative Group, evaluated performing sputum cytology and chest radiographs every 4 months compared to annual sputum cytology and chest radiograph over 6 years [10]. After undergoing baseline chest radiograph and sputum cytology, 10,993 male patients greater than 45 years of age with at least one pack per day smoking history were enrolled between 1971 and 1976 and randomized to the two study groups. Screening resulted in increased lung cancer detection (206 new cancers in screening group vs. 160 in the control group) with increased detection of resectable tumors (46% in study group compared to 32% in control group). However, the overall lung cancer-related mortality was not improved (3.2/1000/year in intense screening group vs. 3.0/1000/year in control group) [10,11].

Further analysis of lung cancer screening with chest radiograph was addressed with the larger patient cohort enrolled in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial. This large randomized clinical trial was designed to evaluate clinical outcomes regarding screening for several cancers. For lung cancer screening, 154,901 participants without a prior history of a PLCO cancer, prior pneumonectomy, or currently undergoing cancer therapy were enrolled between 1993 and 2001 and randomized to either continued routine care or annual posterior–anterior chest radiograph screening at

* Corresponding author. Ronald Reagan UCLA Medical Center, Department of Radiology, 757 Westwood Plaza, Ste 1621, Los Angeles, CA, 90095-1721. Tel.: +1-310-267-8708.
E-mail address: kruchalski@mednet.ucla.edu (K. Ruchalski).

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baseline with sequential annual follow-up chest radiograph for the next 3 years. Both cohorts were subsequently followed for up to 13 years after enrollment. Chest radiograph screen-detected lung cancers were more likely to be less advanced stage disease, with 50% of the tumors being Stage I (compared to 27% Stage I detection in the usual care group). Unfortunately, no significant reduction in lung cancer-related mortality with chest radiograph screening was detected, with a cumulative lung cancer mortality rate (per 10,000 person–years) of 14.0 in the intervention group versus 14.2% with usual care [12].

The above studies provide a historical outline of the initial search for a lung cancer screening tool. Although these studies demonstrated an increase in early cancer detection, the inability to demonstrate improved patient survival prevented the implementation of screening chest radiography for lung cancer.

2.2. Chest computed tomography (CT)

Technological advances in CT, including increased availability and faster and lower dose imaging techniques naturally paved the way for CT as a possible method of early lung cancer detection. Numerous studies have since evaluated the use of low-dose CT in lung cancer screening (Table 1).

Table 1
Evidence for LDCT: randomized controlled trials with LDCT

Study, screening date	No. of participants and demographics	Screening method	Screening time points (months)	Lung cancers detected	Follow up (years)	Adverse events	Lung cancer mortality
NLST (2002–2007) RCT (ref#)	55–74 years ≥30 pack–years in current or former smokers (quit within last 15 years) LDCT (n=26722) T0 n=26,309 T1 n=24,715; T2 n=24,102 CXR (n=26732) T0 n=26,035 T1 n=24,089 T2 n=23,346	LDCT versus CXR	0, 12, 24	LDCT T0 n=270 T1 n=168 T2 n=211 Total n=649 CXR T0 n=136 T1 n=65 T2 n=78 Total n=279	6.5	Death within 60 days after most invasive diagnostic procedure CT n=10 CXR n=11	Relative reduction in rate of death from lung cancer with LDCT screening of 20.0% (95% CI, 6.8 to 26.7; P=.004)
NELSON (2003–2006) RCT (ref #)	50–75 years ≥15 cigarettes per day for more than 25 years OR ≥10 cigarettes per day for more than 30 years Former smokers quit in last 10 years LDCT (n=7915) T0 n=7135 T1 n=6890 T2 n=6538 No screening (n=7907)	LDCT versus no screening	0, 12, 30	LDCT T0 n=62 T1 n=53 T2 n=72 Total n=187	8.16	Lung surgery performed for benign lesion (n=47; 27%) 17% of major complications and 21% of minor complications were for benign lesion No 30 day morality after thoracotomy or VATS	Ongoing trial, not yet available
DANTE (2001–2006) RCT (ref #)	Male 60–75 years ≥20 or more pack–years LDCT (n=1276) T0 n=1276 T1 n=1114 T2 n=842 T3 n=562 T4 n=251 Control (n=1196) T0 n=1196 T1 n=1069 T2 n=742 T3 n=442 T4 n=174	All: baseline CXR and sputum cytology LDCT versus annual physical exam	0, 12, 24, 36, 48	LDCT Total n=60 (4.7%) Control Total n=34(2.8)	3	Lung surgery performed for benign lesion (n=12; 18%)	No significant benefit Lung cancer mortality LDCT=20 (1.6%) Control=20 (1.7%) P=.84
DLCST (2004–2006) RCT (ref #)	50–70 years Current or former smokers ≥20 or more pack–years Former smokers quit in last 10 years LDCT (n=2052) T0 n=2047 T1 n=1976 T2 n=1944 T3 n=1982 T4 n=1851 Control (n=2052) T0 n=2052 T1 n=1953 T2 n=1877 T3 n=1838 T4 n=1820	LDCT versus no screening	0, 12, 24, 36, 48	LDCT T0 n=17 T1 n=11 T2 n=13 T3 n=12 T4 n=16 Total n=69 Control T0 n=1 T1 n=4 T2 n=6 T3 n=7 T4 n=6 Total n=24	4.76	1 death after thoracotomy for Stage I adenocarcinoma	No significant benefit Lung cancer mortality LDCT=15 (0.73%) Control=11 (0.54%) P=.428

NELSON=Dutch Belgium Randomized Lung Cancer Screening Trial.