Systematic Review of Lung Cancer Screening Trials with low dose computed-tomography: 2017 update

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Abstract

Lung cancer is the leading cause of death among all cancers and is the third most common cancer in both men and women. This makes lung cancer screening an attractive proposition. This systematic review of randomized controlled trials is carried out to determine whether the clinical trial data is for or against lung cancer screening. We searched PubMed database to find randomized controlled trials and controlled clinical trials within the last fourteen years to find studies which looked at how low dose computed-tomography (LDCT) screening affects lung cancer mortality. We included eight trials in this review, seven of which were statistically lower powered studies that found no significant decrease in mortality in patients with lung cancer when using low-dose CT. However, the high-powered national lung screening trial (NLST) published in 2011 with 53,454 participants found a significant decrease in death from lung cancer when screened with low-dose CT compared with chest x-ray screening. Currently, we await results from the NELSON trial to further strengthen this conclusion. However, there are also other factors which need consideration when electing to undergo lung cancer screening such as, cost-effectiveness, psychological consequences, radiation exposure and unnecessary invasive procedures.

Keywords: low dose computed-tomography, lung cancer, screening

Introduction

Lung cancer is the leading cause of death among all cancers and is the third most common cancer in both men and women[1]. Lung cancer accounts for approximately 28% of all cancer cases and has one of the lowest 5 year survival rates of any cancer at approximately 16.8%[1]. Smoking is the primary cause of lung cancer and primary prevention should be the principal focus of prevention. However, smoking cessation is likely to have a limited impact in the short term because it takes approximately 20-40 years to show any major effect, which makes secondary prevention an attractive proposition[2]. Early detection of lung cancer has shown better 5-year survival rates[3][4]. Screening modalities include chest x-ray, sputum cytology and recently low-dose computed tomography. Traditionally many studies have researched the efficacy of CXR combined with sputum cytology on early detection, however these have shown to be statistically insignificant[5][6][7]. However, advances in computed tomography technique have reduced the radiation exposure by the use of low dose CT. Which is now reported to have approximately the same radiation dose as mammography[8] and has renewed the interest in lung cancer screening. This systematic review was to determine whether data was for or against screening with LDCT.

Methods

Using the PubMed Library, we searched "low dose CT lung cancer screening" with criteria "controlled clinical trial" and "randomized controlled trial". We set our article date limit from 01/01/1990 to 12/31/2016. We also referred to the Cochrane Systematic Review 2013 and followed up with smaller ongoing studies in Europe. From our search, we will be discussing the Lung Screening Study, the MILD trial, the DANTE trial, DEPISCAN study, the National Lung Screening Trial (NLST), the DANISH trial, the ITALUNG trial, and the UKLS pilot.

Results

Lung Screening Study

The LSS was a pilot study designed to pave way for larger future studies such as the NLST. This study included 1,660 participants for the low dose CT arm and 1,658 participants in the chest radiography arm. Individuals had to be between 55 and 74 years old, have a minimum 30 pack year smoking history, and be a current smoker or a former smoker who had quit within the last 10 years. Any non-calcified nodule greater than 4 mm was considered to be a positive screening. Other suspicious nodules such as spiculated nodules less than 3 mm would also qualify for positive screens. For the initial screening, the low dose CT group had a positive rate of 25.8% while the chest radiography group had a positive rate of 8.7%. Individuals with positive screens were then referred to their personal health care providers for follow up; the LSS did not have any specific diagnostic follow-up algorithm. 40% of the low dose CT and 50% of the chest radiography group had a follow-up chest CT. About 0.57% of the low dose CT and 0.68% of the chest radiography arms were diagnosed with lung cancer within a year since the initial screening. Six subjects, five with a lung cancer diagnosis, encountered complications that were likely related to diagnostic follow-up procedures. Overall, the LSS showed that twice as many cases were diagnosed in the low dose CT arm than the chest radiography arm, with the number of stage 3 and stage 4 cancers also being higher in the low dose CT arm[9].

The MILD trial

The trial compared lung cancer incidence and mortality in three groups, control, annual low

dose CT and biennial low dose CT. There was a total of 4,099 subjects, with 1723 in the control group, 1186 in the biennial low dose CT group, and 1190 in the annual low dose CT screening group. The cumulative 5-year lung cancer incidence rate was 0.311% in the control group, 0.457% in the biennial, and 0.62% in the annual low dose CT group; lung cancer mortality rates were 0.109%, 0.109%, and 0.216%, and total mortality rates were 0.310%, 0.363%, and 0.558%, respectively. Specifically, the number of lung cancer cases diagnosed were 20 in the control group, 25 in the biennial low dose CT and 34 in the annual low dose CT. Lung cancer mortality were 7 in the control, 6 in the biennial and 12 in the annual low dose CT[10]. Total mortality observed in the annual low dose CT arm at 5 years was similar to that observed in the pilot study. There was no evidence of a protective effect of annual or biennial low dose CT screening. Likewise, a meta-analysis of the four published randomized trials showed similar overall mortality in the low dose CT arms compared with the control arm. Even though the number of deaths did not show statistical significance, lung cancer and total mortality were still higher in the annual low dose CT arm when compared with the control arm. Additionally, the decreased mortality with LDCT shown by the NLST trial disappears with a pooled analysis of the four published trials Dante, NLST, MILD, and DLCST[10].

The DANTE trial

This was a study by the Humanitas Research Hospital in Milan, Italy. There were 1,264 subjects recruited into the study. To meet criteria, subjects had to be male smokers, or former smokers of at least 20 pack year who had quit no more than 10 years before the recruitment process. Recruitment period was from March 2001 to February 2006, subjects ages ranged from 60 to 74 years old. All subjects in the study received a baseline chest XR In the screening arm, 37% was positive and 28% of those underwent further testing. 17.7% of the subjects who underwent surgical procedures did not show any cancer. Additionally, 3.3% died postoperatively, but no deaths were associated with surgical procedures for benign lesions. In the screening arm, 30.76% more were diagnosed with lung cancer, however the mortality rate was unchanged when compared to the control arm. There was no evidence of a protective effect of annual or biennial LDCT screening. Although the DANTE trial has a control arm while the NLST does not, the DANTE trial has limited statistical power. Therefore, it is important to gather data from all randomized trials with an intervention-free control arm, such as the NELSON study, to provide answers for LDCT lung cancer screening[11][12].

The DEPISCAN trial

A total of 765 subjects were enrolled in this study, 385 participants were in the low dose CT arm and 380 were in the chest radiography arm. To be eligible for the study, subjects had to be 50 to 75 years old, asymptomatic current smoker, or former smoker who had quit within 15 years from enrollment, and have consumed $\geq$ 15 cigarettes per day for at least 20 years. For participants that screened positive for non-calcified nodules on low dose CT, specific guidelines were implemented regarding follow-up protocol. In the low dose CT arm, 45.2 % screened positive for non-calcified nodules while 7.4% screened positive in the chest radiography arm. Lung cancer was diagnosed in 2.4% of the low dose CT arm and in 0.3% of the chest radiography arm.

Three thoracotomies were performed on benign lesions, which were formerly suspected to be lung cancer. Overall, this study shows that low dose CT is able to detect non-calcified nodules much more often than chest radiography. For future studies and screening programs, it is important to have a better defined eligibility criteria to select appropriate high-risk subjects for screening[13].

The DANISH trial

This Netherlands study recruited a total of 4,104 participants with ages between 50 to 70 years old. To meet the criteria, subjects had to have a minimum 20 pack-years of smoking. If subjects were former smokers, they must have had to quit after age 50 and within the past 10 years. More specifically, their FEV1 value had to be at least 30% of the predicted value, and subjects had to be able to climb 36 steps without pausing. Subjects were then randomized into two groups: one group with five annual low-dose CT scans, and one group with no screening[14]. By the end of the study, there were 39 deaths from lung cancer in the screening group, and 38 deaths from lung cancer in the control group. There were more early stage and stage IIIa cancers that were detected in the screening group than the control group. Interestingly, more of the highest stage cancers were found in the control group than the screening group. The screening group had almost double the number of lung cancer diagnoses when compared to the control group. However, there was no significant difference in the number of high-stage cancer, as they were mainly early-stage adenocarcinomas. Subjects with normal lung function had a longer volume doubling time for adenocarcinomas when compared with subjects with COPD. Therefore, limiting LDCT to individuals with COPD could reduce the problem of overdiagnosis. Although the DLCST is statistically underpowered, the results do not agree with the recommendations of LDCT lung cancer screening as found in the NLST. For future studies, a focus on age, smoking history and COPD status when selecting candidates can reduce overdiagnosis[14].

The ITALUNG Trial

For the ITALUNG trial, participants were recruited via mail invitations. They had to be asymptomatic smokers or former smokers with at least a 20 pack year history, and aged 55 to 69 years with no history of lung cancer. 1,613 participants were in the low dose CT arm and 1593 participants were in the control arm. Low CT screening was able to detect cancers in 30.3% of subjects at baseline and 15.7% subjects at the three annual repeated screenings. Of the screen-detected non small cell lung cancer (NSCLC), 66% were in stages IA or IB. Adenocarcinoma accounted for 56% of the NSCLC at first screening round and 88% of NSCLC at subsequent repeat screening rounds. Due to the high cost of low dose CT and low detection rate, inclusions of sputum or blood biomarkers should be considered[11]. Lung tumors were detected in 1.5% of subjects at baseline and 0.5% of subjects subsequently. The ITALUNG trial had a rate of 10% for surgery of benign lesions, which is significantly lower than those reported in a majority of the other screening studies. This is due to their strict adherence to a protocol which includes follow-up LDCT with 1 month of antibiotic therapy, FDG-PET, and CT-guided FNAB prior to making the decision for surgery. A unique feature of the protocol is the antibiotic therapy before 1 month follow-up LDCT, which should decrease the rate of unnecessary subsequent screening by revealing the active inflammatory incident nodules. Subsequent studies should continue to follow strict

protocols in order to avoid unnecessary surgeries and procedures[11].

UKLS pilot

This pilot study recruited a total of 4,061 subjects for the trial, ages 50 to 75 years old. Of the 1,994 individuals who were in the CT group, lung cancer was diagnosed in 2.1% of subjects. Specifically, of the 42 low dose CT screening-detect cancers, 25 were adenocarcinomas, 12 were squamous cell carcinomas, 3 were small cell carcinoma, 1 was typical carcinoid, and 1 was bronchogenic carcinoma. About 85% of the detected cancers were in stage I or stage II. 83% of the subjects diagnosed had surgery as their primary treatment. This pilot has shown that low dose CT screening can detect lung cancers at an early stage and most of those cases had potentially curative treatments. Although the UKLS was only a single screen, the results yielded were similar to the NLST. Since this is only a pilot study, it does not have enough power to obtain results on mortality comparisons of low dose CT vs. no screening. It is important to continue following up with data received from the UKLS trial[15].

National Lung Screening Trial

This study included 53,454 participants from 33 US medical centers starting from August 2002 to April 2004. 26,722 subjects were enrolled in the low dose CT group, and 26,732 subjects were enrolled in the chest radiography group. To meet criteria for the study, participants had to be asymptomatic, have had at least 30 pack year history, had never been diagnosed with lung cancer and have not had chest CT within 18 month of enrollment. Researchers found that low dose CT screening detected 645 cases per 100,000 of lung cancer, while the radiography only detected 572 cases per 100,000. The results from the NLST showed an absolute stage shift, a 20% reduction in lung cancer mortality, and a 6.7% decrease in all-cause mortality with three rounds of low-dose CT screening versus plain chest radiography[16]. Lung cancer was diagnosed in 1.1% of participants who received low dose CT screening and 0.7% in participants who had chest radiographic screening. As for diagnostic follow-up procedures, at least one diagnostic procedure was performed in 90.4% of participants in the low-dose CT group and 92.7% of participants in the radiography group. For each cancer stage, the frequencies of treatment types did not differ significantly between low dose CT and radiographic screening groups[17]. However, the results also revealed a worrisomely large number of false-positive screens; the rate of positive screening tests was 24% in the CT screening group, and 96% of these turned out to be false-positive results[16]. There were some inconsistencies found in this study compared to previous results. The prevalence of lung cancer was only 1.1%, the lower end of the reported range in prior studies. However, this may be due to the healthy-volunteer effect, a younger study population, and a high proportion of former smokers[17].

Table 1 and 2 below summarize the results of randomized controlled clinical trials utilizing low dose computed tomography in screening for lung cancer.

Table 1: summary of randomized controlled clinical trials utilizing low dose computed tomography in screening for lung cancer with study size, age, eligibility criteria and screening intervals

Study	Date Range	Number of participants	Age group	Study Arms	Eligibility Criteria	Screening intervals
Lung Screening Study	2000-2004	3,318	55-74 years	no screening, annual LDCT screening	ages 55 to 74 years old, have a minimum 30 pack year smoking history, and be a current smoker or a former smoker who had quit within the last 10 years	1 repeated LDCT
The MILD Trial	2000-2005	4,099	median age 57-58 years	no screening, annual LDCT screening, biennial LDCT screening	ages 49 or older, current or former smokers who had quit within 10 previous years, a minimum history of 20 pack-years, and no history of cancer within past 5 years	annual and biennial repeated LDCT for a maximum of 6 years
The DANTE Trial	2001-2006	2,472	60-74 years	no screening, annual LDCT screening	male smokers or former smokers of at least 20 pack-years who had quit less 10 years before recruitment	4 annual repeated LDCT rounds
The DEPISCAN Trial	2002-2004	765	50-75 years	chest radiography, annual LDCT screening	50 to 75 years old, an asymptomatic current smoker or former smoker who had quit within 15 years from enrollment, and have consumed > 15 cigarettes per day for at least 20 years.	2 annual repeated LDCT or chest radiography rounds
National Lung Screening Trial	2002-2010	53,454	55-74 years	chest radiography, annual LDCT screening	asymptomatic with a history of at least 30 pack-years, currently smokers or former smokers who had quit within previous 15 years	3 annual repeated LDCT or chest radiography rounds
The DANISH Trial	2004-2006	4,104	50-70 years	no screening, annual LDCT screening	current or former smokers who have quit after age 50 and within previous 10 years, a minimum smoking history of 20 pack-years, FEV1 of at least 30% predicted value, ability to climb 36 steps without pausing	4 annual repeated LDCT rounds
The ITALUNG Trial	2004-2016	3,106	55-69 years	no screening, annual LDCT screening	asymptomatic smokers and former smokers with a smoking history of at least 20 pack years, and no history of cancer (besides non-melanoma skin cancer)	3 annual repeated LDCT rounds
UKLS Pilot	2010	4,061	50-75 years	no screening, LDCT screening	risk of $\geq$ 5% of developing lung cancer over next 5 years	no repeats, 1 year repeat, or 3 months repeat depending on nodule category

Table 2: summary of randomized controlled clinical trials utilizing low dose computed tomography in screening for lung cancer showing positive screening rate, lung cancer diagnoses/ detection rates and false positivity rate

-Study	Positive Screening Rate in LDCT	Lung Cancer Diagnoses by LDCT	Lung Cancer Detection rate by LDCT	False Positive Rates of All Positive Scans
Lung Screening Study	25.80%	40	1.90%	-
The MILD Trial	14%- annual 15%- biennial	49	1.30%	-
The DANTE Trial	37.30%	66	2.30%	-
The DEPISCAN Trial	45.20%	8	2.40%	-
National Lung Screening Trial	0.242	649	0.026	0.964
The DANISH Trial	3.80%	69	3.60%	0.814
The ITALUNG Trial	0.196	41	3.10%	0.961
UKLS Pilot	5.70%	42	1.70%	0.632
Average	**18.55%**	**-**	**2.30%**	**-**

Discussion

Lung cancer is the leading cause of death among all cancers and is the third most common cancer in both men and women. It accounts for an estimated 1.3 million deaths each year, representing 28% of all deaths from cancer[1]. Smoking remains the largest contributor to developing lung cancer despite efforts of primary prevention. Detecting lung cancer at an early stage has shown to increase 5- year survival rates[3][4]. Unfortunately, early stages of lung cancer usually do not present with obvious signs and symptoms. It is only until many years later when the cancer has progressed to late stage does the patient present with symptoms[18].

Although LDCT screening has shown to reduce lung cancer mortality in the NLST, there are many factors that affect patients who undergo this screening. As described by Rasmussen *et al* (2015), LDCT lung cancer

screening trials induced more negative psychosocial reactions in both the CT and the control group when compared with the baseline psychosocial profiles[19]. Additionally, the control group experienced more negative consequences than the CT group, which could be explained by the reassurance that comes with normal screening results in the CT group. Both positive and negative test results can affect participants in negative ways. A negative screening result might lead to a sense of reassurance. This can cause individuals to underestimate the influence of lifestyle interventions, specifically smoking. While a positive test result can reduce the risky behaviors, it brings on stress and anxiety to both the patients and their families. Since more than 300 individuals need to be screened to avoid one lung cancer death, many screened participants may be potentially exposed to unwarranted negative psychological effects[20].

In particular, false positive results can also have psychological consequences and are especially harmful since they may result in unnecessary procedures like biopsy or thoracotomy. In the NLST, 23.3% of all CT screenings resulted in false-positives, while only 3.6% of the screenings led to a diagnosis of lung cancer. Specifically, 2.7% of participants with false-positive results faced complications from diagnostic work-up procedures. However, the NELSON trial reports an overall false positive rate of only 1.2%. The NELSON trial suggests follow-up CT scans for smaller nodules rather than immediate referral which would eventually lead to unnecessary diagnostic procedures and more false positives. Unfortunately, as false-positive results decrease so does the sensitivity for detection[20].

Another consideration which must be taken into account is how screening for lung cancer effects smoking habits. This has been a topic of controversy with two schools of thought. First thought being that screening tests promote smoking cessation due to participants being more cautious of their health. It also provides healthcare professionals with an opportunity to counsel patients on harms of smoking. The other thought is that participants feel a false sense of security and feel protected by screening which demotivates them to quit smoking. Some studies have called this a “license to smoke” and is one of the concerns of implementing lung cancer screening[21]. The DLCST published 5-year analysis regarding smoking habits in participants of their study. The results showed no significant difference in smoking cessation between participants in the CT screening group and the control group[22]. Smoking cessation rate was between 10-11% in both groups which is higher when compared to the general population[22][23]. This shows participation in a screening trial regardless of which group encourages participants to quit smoking. Thus, lung cancer screening seems to be a teachable moment for smoking cessation since participants seem to be more motivated to quit at this time[23]. Counselling along with nicotine replacement therapy should be integrated as part of future screening programs. This implementation will further help decrease mortality in participants[24].

One of the more important factors is cost-effectiveness of CT screening. According to Black *et al* (2014) it was found Medicare reimbursement for chest CT scan was $285, while chest radiograph was only $24. Overall, screening with low dose CT costs $1,631 per person and provided an additional 0.0316 life-years per person[25]. Compared to no

screening, LDCT costs an additional $81,000 per quality-adjusted life year gained. This falls below $100,000, the threshold level that experts consider to be of reasonable value in the United States[16]. However, the cost-effectiveness of LDCT screening will ultimately depend on how screening will be implemented outside of the trial.

Another pertinent component to consider is the location of screening centers. While larger academic centers may be able to provide consistency in reading of the CT scans, they may not be easily accessible to patients who live in smaller towns further away. However, in small community hospitals, there may not be an established method in reading CT scans and consistency in the steps to take with positive results. Therefore, it is essential that all future screening programs follow a system, such as the Lung-RAD scoring system defined by the American College of Radiology (ACR). A category 1 score is negative, where the low dose CT scan shows no nodules or nodules with specific calcifications and would recommend continuation of annual low dose CT screening. A category 2 has benign appearance or behavior, CT scan shows solid nodules < 6 mm or new nodules < 4 mm, and recommendations are also annual low dose CT screenings. Category 3 nodules are probably benign but does have a small likelihood of becoming active cancer, these have nodules $\geq$ 6 but < 8 mm where the patient would have a follow up LDCT in 6 months. Category 4 is suspicious and broken into 3 subgroups: 4A are solid nodules $\geq$ 8 mm and < 15 mm, and a 3 month low dose CT is recommended for the patient; 4B have solid nodules $\geq$ 15 mm; 4X has additional findings that increases the suspicion of malignancy, both requiring chest CT with or without contrast and potential tissue sampling.

One example of an established lung cancer screening program in a community hospital is at Orange Regional Medical Center in Middletown, New York, where the authors currently work. The program started about 3 years ago and became accredited by the center for medicare and medicaid services (CMS) in April of 2016. Patients must meet the same criteria as prescribed by CMS in order to be eligible for enrollment. This includes age 55 to 77 years old, asymptomatic, a smoking history of at least 30 pack-years, currently smoking or former smoker who has quit within the last 15 years, and received a written order for LDCT lung cancer screening. Currently, the program has enrolled around 80 eligible patients. It is imperative that all programs continue to establish and follow eligibility criteria and use scoring systems for evaluating positive scans and management steps to follow. This will help reduce unnecessary studies and procedures while providing patients with the best preventative care possible.

Several randomized controlled trials have been performed to investigate the effectiveness of LDCT on lung cancer mortality. The initial seven studies were statistically lower powered studies and found no significant decrease in mortality in patients with lung cancer when using low-dose CT. The National Lung Screening Trial (NLST) conducted in America screened participants between the ages of 55-74 with a minimum of a 30 pack year history and are current smokers or who have quit less than 15 years ago. The results were profound showing a 20% reduction in lung cancer mortality for LDCT compared with CXR, as well as a 6.7% all-cause mortality reduction[16]. Since then

many medical associations have used the NLST criteria and have issued guidelines for LDCT screening in high risk patients[26]. Included in these medical associations is the United States Preventive Services Task Force (USPSTF), which has recommended LDCT screening for lung cancer; annual screening for men and women aged 55–80 years with a smoking history of at least 30 pack-years, who currently smoke or quit smoking within the past 15 years. Despite LDCT screening being implemented in the USA as a guideline, it remains a topic of controversy. Other studies conducted in Europe have found contrary results to the NLST. In fact, as stated in the MILD trial, the decreased mortality shown in the NLST with LDCT disappears with pooled analysis of the four published trials Dante, NLST, MILD, and DLCST[10]. However, it is important to note that other trials conducted to date have significantly lower power compared to the NLST. This important distinction should make one critical of the results found in the other trials. We must follow up with other statistically powerful studies to make final conclusions on reduction in lung cancer mortality with LDCT screening. We are currently awaiting the final results from the 10 year long NELSON Trial in which 7557 high risk participants underwent CT screening and 7907 did not[27]. This trial has a similar criteria to the NLST for selecting high risk lung cancer participants. This trial along with the NLST will help shape our understanding of LDCT screening on lung cancer mortality.

Conclusion

In conclusion, the results of the NLST has allowed many medical associations including the United States Preventive Services Task Force (USPSTF) to issue guidelines as a standard for lung cancer screenings. Other statistically low power trials have failed to detect any significant decrease in mortality by low dose computed tomography screening. In fact, some have found contrary results to the national lung screening trial (NLST). The NELSON trial, similar to the NLST, is a statistically high power trial which compares mortality in high risk populations who received LDCT screening with those who didn't. We eagerly await the results of the NELSON trial which may help strengthen the conclusions made in the NLST. We also keep in mind of the consequences of LDCT which also need to be further evaluated and are worth considering when electing to undergo LDCT screening, such as psychological consequences, cost, radiation exposure, unnecessary invasive procedures. Following strict guideline and protocols can help reduce overdiagnosis, unnecessary procedures, and negative psychosocial effects as mentioned above.

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