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Screening for Lung Cancer with Low-Dose CT Scans

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Abstract

Lung cancer is the leading cause of cancer deaths in males and the second leading cancer cause of death in females. The 5-year survival of all lung cancer patients in the United States is 16%. Only 15% of new lung cancers are stage I at the time of diagnosis, and over 50% of patients have stage IV lung cancer at diagnosis. Most lung cancers are not diagnosed until the patient presents with signs or symptoms of disease, and these are usually due to advanced-stage disease. If we are going to increase the cure rate for lung cancer, then more cases must be detected while the patient is asymptomatic and before the cancer has spread. Screening of high-risk individuals with low-dose computed tomography (LDCT) may help in diagnosing the lung cancer at earlier stages. Screening with LDCT in high-risk individuals is becoming the standard of care in the United States and, along with smoking cessations, offers the best opportunity for decreasing a substantial number of lung cancer deaths. In this article, recent manuscripts about lung cancer screening with LDCT have been reviewed.

Keywords: Low-dose CT scan, lung cancer, screening

INTRODUCTION

GLOBOCAN 2012 reported that lung cancer is the leading cause of cancer deaths in males and the second leading cancer cause of death in females. Lung cancer accounts for 19.4% (1.6 million) of all cancer deaths in 2012 (1). GLOBOCAN reports data by countries, including Turkey. In Turkey, lung cancer causes 25% of all new cancers in men and accounts for 32% of all cancer deaths. In Turkish women, lung cancer accounts for 7% of all new cancers and 11% of cancer deaths (1). These estimates come from high-quality regional data, but coverage is lower than 10% of the country.

In 2014, it is estimated that there will be 224,000 new cases of lung cancer in the United States and 159,000 deaths from lung cancer. Lung cancer accounts for 28% of all cancer deaths in males and 26% of cancer deaths in females (2). The 5-year survival of all lung cancer patients in the United States is 16%. Only 15% of new lung cancers are stage I at the time of diagnosis, and over 50% of patients have stage IV (incurable) lung cancer at diagnosis. Most lung cancers are not diagnosed until the patient presents with signs or symptoms of disease, and these are usually due to advanced-stage disease. If we are going to increase the cure rate for lung cancer, then more cases must be detected while the patient is asymptomatic and before the cancer has spread.

The National Lung Screening Trial (NLST)

The NLST was a screening trial for lung cancer in the United States that randomized 53,454 high-risk individuals to low-dose (radiation) CT (LDCT) or a single-view posterior-anterior chest radiograph for three annual screenings, and then, participants were followed for a median of 6.5 years (3).

Low-dose CT detected more than twice as many lung cancers as the chest radiograph (649 vs. 279) in the 3 years of active screening, and 63% of the lung cancers detected by LDCT were stage IA/B (4, 5). (Figure 1) Screening with LDCT resulted in 20% lung cancer mortality reduction as compared to chest radiography (247 vs. 309 deaths per 100,000 person-years). Additionally, the rate of death from any cause was reduced in the LDCT group by 6.7%. This was the largest randomized prospective lung can-

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cer CT screening trial ever conducted and, to date, is the only lung cancer screening trial to document a mortality reduction with LDCT screening.

Limitations of NLST

Over-diagnosis is generally defined as the detection of a cancer that would never have been detected without screening and never would have led to symptoms or death. Perhaps the best example of this is 1-2 -cm adenocarcinomas *in situ* with an estimated volume doubling time (VDT) of 600 days or longer. In an Italian CT screening trial, slow-growing cancers had a VDT of 400-599 days, and indolent cancers had a VDT of 600 days or longer. Slow-growing or indolent cancers accounted for 25% of the incident lung cancers (Figure 2 a, b) (6).

In the NLST, there were 120 more lung cancers diagnosed on the LDCT versus chest radiograph arm. The estimates of over-diagnosis from a clinical perspective were 18.5% (120/649) or 11% (120/1089) from a public health perspective (7). The comparative modeling study for the US Preventive Services Task Force reported estimates of over-diagnosis with LDCT screening of 8.7%-13.1% (8).

Thoracic operations for benign disease are significant negative to screening for lung cancer. In the first year of NLST, 90 of 297 (30%) of all surgical procedures in the LDCT arm were for benign disease (4). This decreased to 18.9% in the second year and 15.9% in the third year of screening in the LDCT arm. The data suggest that there was a learning curve for physicians and with time, and fewer indeterminate nodules were resected (5).

Screening for Lung Cancer in USA

The eligibility criteria for enrolling in the NLST included age 55-74 years, current or former smokers of at least 30 pack-years, and former smokers could not have quit more than 15 years before entry. It is estimated that only 26.7% of lung cancer patients seen in the USA in any 1 year would have met the criteria for enrollment into the trial (9). Approximately 8.6 million Americans met the NLST criteria for screening in 2010. If LDCT screening were to be fully adopted, then approximately 12,000 lung cancer deaths would be averted each year

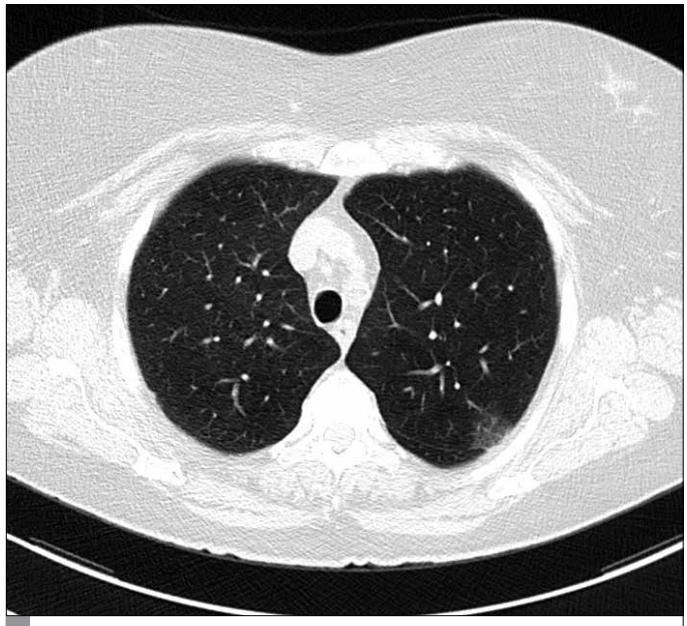


Figure 1. CT scan from a 73-year-old female former smoker. The CT shows a ground glass density lesion that is not visible on chest radiograph. This lesion was resected 15 months after this CT scan and proved to be adenocarcinoma *in situ* (Stage 0).

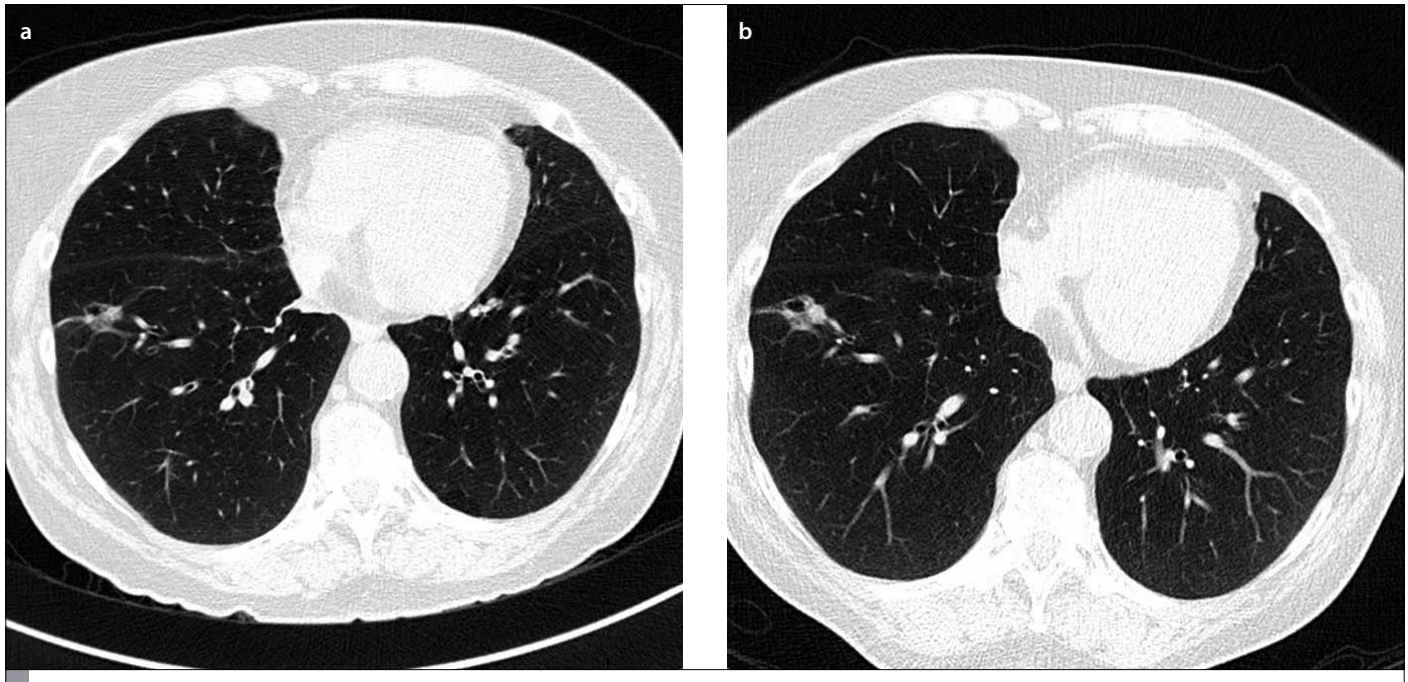


Figure 2. a, b. This low-dose screening CT scan was read out by the radiologist as showing a 1.6 -cm focal course linear density and irregular consolidation in the anterior right lower lobe (a). The patient was followed with CT scans at 4 months and 10 months, and the lesion was stable. A following CT scan 14 months after the initial CT scan demonstrated enlargement and measured 1.9 cm. At resection, it proved to be a low-grade adenocarcinoma, Stage IA (b).

(10). The USPSTF modeling study estimated that 18,000 lung cancer deaths per year might be avoided in the US with LDCT screening (8).

The US Preventive Services Task Force (USPSTF) is an independent panel of non-federal experts in prevention and evidence-based medicine, and it conducts scientific reviews of a broad range of clinical preventive health services, including screening, and develops recommendations for primary care clinicians and health systems. The USPSTF issued a recommendation statement based on the review of screening for lung cancer with LDCT. The USPSTF recommends annual screening for lung cancer with LDCT in adults 55 to 80 years who have a 30 pack-year smoking history and are current smokers or have quit within the past 15 years (11). Individuals should not have health problems that significantly limit life expectancy or are unwilling to have curative lung surgery. The level of this recommendation was Grade B. A Grade B recommendation means that the test is recommended and there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Based on the 2010 Affordable Care Act (Obamacare), those services that receive a USPSTF recommendation of A or B must be provided free of charge by the insurance company to their participant. Medicare (insurance for individuals ≥65 years) is a government insurance, and they may pay for screening with LDCT, but they are not absolutely required to do so based on the USPSTF recommendation. At this time (March 2014), the Centers for Medicare and Medicaid are considering the option of paying for screening with LDCT for lung cancer. A decision is expected later in 2014.

Cost Effectiveness

There have been wide variations in the estimates of cost effectiveness of screening with LDCT. These are based on various models and estimates. Investigators from the Early Lung Cancer Action Project estimated that a single baseline CT scan had a cost effectiveness of $2500 per year of life saved (12). McMahon and colleagues estimated that annual screening of high-risk individuals with a minimum of 20 pack-years of smoking costs between $126,000 and $169,000 per quality-adjusted life-year (QALY) (13). For former smokers, Mahadeva and associates estimated a cost of $2,322,700 per QALY (14). In current smokers, this decreased to $116,300 per QALY.

At the 2013 World Congress on Lung Cancer in Sydney, Australia, Dr. Christine Berg reported on the preliminary analysis of the cost-effectiveness of LDCT screening in the NLST. Compared to no screening, LDCT screening costs $1441 per person and $67,000 per QALY (15). A peer-reviewed publication of these results is anticipated in 2014. This cost per QALY is under the $100,000 per QALY level in the US, indicating good value for the money (16).

The USPSTF analysis of cost-effectiveness did not take into consideration the rate of smoking cessation in the study. Smoking cessation was evaluated in the Dutch-Belgian randomized trial (NELSON) (17). Almost 17% of the trial participants quit smoking. However, the 1-year continued abstinence rates were 12.6% in the screened arm and 14.6% in the control arm. Thus, it appears that participants in a screening trial, regardless of which arm of the study they are in, are highly motivated to quit. In the single-arm Pan-Canadian screening trial, all participants were screened with LDCT. The smoking cessation rate at 2 year was 20% (personal communication with PI: Dr. Stephen Lam). Accordingly, if a smoking cessation rate of 10-20% were to be included in the cost analysis of LDCT screening, it would lower the cost for QALY. Using modeling data, investigators have estimated that offering smoking cessation with annual LDCT screening would improve the cost-effectiveness of screening by 20-45% (18).

Screening High-Risk Individuals

Investigators evaluated the efficacy of LDCT screening in the NLST based on the 5-year risk of death from lung cancer death (19). The risk was divided into five quintiles of risk. They were able to show that 88% of the prevented lung cancer deaths occurred in the top three quintiles of risk (top 60%). Likewise, the number of participants needed to be screened to prevent one lung cancer death decreased to 208 versus 302 for all five quintiles. The number of false-positive LDCT scans to prevent one lung cancer death also decreased significantly. Similar trends in trends in lung cancer mortality ratios and mortality differences were observed with risk quintiles based on either risk of lung cancer death or the predicted risk of lung cancer (19, 20).

Tammemagi and colleagues developed and validated a lung cancer risk prediction model based on data from North Americans enrolled in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial (JNCI Study). They modified the risk prediction model of PLCO to make it applicable to the NLST participants (20). The use of the new PLCO risk model was more sensitive than the NLST eligibility criteria for lung cancer detection. The PLCO risk model had improved sensitivity (83% versus 71%) without loss of specificity (62.9% versus 62.7%). Overall, the PLCO risk model identified 81 more of the 678 lung cancers. The lung cancer risk prediction calculator is available online at http://www.brocku.ca/lung-cancer-risk-calculator.

Screening Schedules

The NLST performed LDCT once a year for three scans and then followed participants for an additional 6.5 years without screening. The yearly screening interval was an empirical decision based on the usual screening interval for other screening tests (*e.g.,* mammography). Limiting the screening to 3 years was based on costs and financial limitations of funding the study (3). In comparison, the NELSON trial performed baseline screening with LDCT and then again at 1 year and 3 years. They skipped the 2-year screening time point. The mortality results of the NELSON trial have not yet been reported (21). Accordingly, no conclusion can be made on the efficacy of the NELSON trial screening interval. Recently, the Cancer Care Ontario's Program on Evidenced-Based Care has recommended that persons at high risk for lung cancer should be screened for 3 consecutive years and then once every 2 years after each negative scan (22).

The comparative modeling study for the USPSTF evaluated results of screening every 3 years, every 2 years, and yearly. The eight most efficient screening programs all involved yearly screening with LDCT scans (8).

CONCLUSION

It is estimated that a significant proportion of lung cancers in the world would be prevented if existing programs for tobacco control were to be implemented. These include raising the price of cigarettes

and other tobacco products (*e.g.,* hookahs), banning smoking in public, restricting advertising of tobacco, and treating tobacco dependence (23). Since the publication of the first United States surgeon general report on smoking and death in 1964, it is estimated that tobacco control in the USA has been associated with avoidance of 8 million premature deaths and an extended mean life span of 19-20 years for each beneficiary (24).

Smoking cessation should be part of any lung cancer screening program with LDCT. Screening is an opportunity to educate individuals as to the risks of smoking and expose them to methods of smoking cessation and programs to assist in their efforts to quit smoking, such as the US Centers for Disease Control website, http://www.cdc.gov/tobacco/campaign/tips/.

Screening with LDCT in high-risk individuals is becoming the standard of care in the United States and, along with smoking cessation, offers the best opportunity for decreasing a substantial number of lung cancer deaths.

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