Title
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Permalink
https://escholarship.org/uc/item/1ng544vm

Journal
Journal of General Internal Medicine, 36(10)

ISSN
0884-8734

Authors
Desai, Aakash
Prasad, Vinay

Publication Date
2021-10-01

DOI
10.1007/s11606-021-06806-5

Peer reviewed

VIEWPOINT

Low-Dose Computed Tomographic Screening for Lung Cancer: Time to Implement or Unresolved Questions?
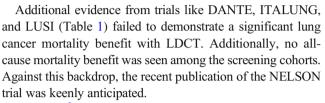
Aakash Desai, MBBS, MPH[1] and Vinay Prasad, MD, MPH[2,3]

[1]Department of Internal Medicine, University of Connecticut, Farmington, CT, USA; [2]Department of Medicine, University of California, San Francisco, San Francisco, CA, USA; [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA.

Lung cancer results in more cancer deaths than breast, prostate, colorectal, and brain cancers. Since most lung cancer patients are identified at advanced stages, with a 5-year survival of <15%, the prospect of screening has garnered much attention. Yet, early results were disappointing. Trials investigating the utility of chest radiography (CXR) and sputum cytology for screening failed to demonstrate a mortality benefit. However, more recent studies assessing low-dose computed tomography (LDCT) have yielded promising results, spurring enthusiasm. These trials also have quantified the magnitude of potential benefit, but also suggest continued unresolved questions.

In 2011, the National Lung Screening Trial (NLST)[1] demonstrated a 20% (95% CI, 6.8 to 26.7; *P* = 0.004) relative reduction in mortality from lung cancer, as well as improved all-cause mortality by 6.7% (95% CI, 1.2 to 13.6; *P* = 0.02) with LDCT over CXR. Concerns were raised however that the trials' non-standard control arm may mask potential harms, as well as the fact that the significance of overall mortality in the initial publication was contingent on a numerical imbalance in non-lung cancer deaths. In other words, a difference in non-lung cancer deaths that happened to favor the CT screening arm was necessary for the NSLT to have an overall mortality benefit. For this reason, it is not surprising that in an extended follow-up, the overall mortality benefit is no longer significant[2] (RR 0.97 (95% CI: 0.94–1.01); the difference in the number dying (per 1000) is 4.2 (95% CI: –2.6 to 10.9, *p* =0.18). Despite these caveats, the United States Preventive Service Task Force (USPSTF) and Canadian Task Force on Preventive Health Care endorsed annual screening LDCT for lung cancer in adults aged 55 to 80 years with a 30 pack-year smoking history who currently smoke or have quit within the past 15 years.

Additional evidence from trials like DANTE, ITALUNG, and LUSI (Table 1) failed to demonstrate a significant lung cancer mortality benefit with LDCT. Additionally, no all-cause mortality benefit was seen among the screening cohorts. Against this backdrop, the recent publication of the NELSON trial was keenly anticipated.

NELSON[6] compared a strategy of four annual screenings with LDCT to no screening among male smokers 50–74 years old, with >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years and have quit less than 10 years ago. The average number of screening CT scans in the intervention arm was 3.43. At a median follow-up of 10 years, NELSON found that lung cancer mortality was significantly lower among at-risk individuals who underwent LDCT compared with no screening among high-risk patients (2.43% vs 3.17%).

At the same time, NELSON raises important concerns. Lung cancer mortality requires adjudication, and attribution of death is not an exact science.[7] An endpoint less prone to interpretation is death from any cancer. In NELSON, this endpoint occurred in 499 of 6612 (7.54%) control arm participants and 478 of 6583 (7.26%) intervention arm participants, a difference that fails to meet nominal significance.

All-cause mortality is resistant to observer interpretations, and here too NELSON provides a cautionary note. Despite the 0.74% reduction in lung cancer death, no difference was seen in all-cause mortality between the two groups (13.76% (control) vs 13.93% (screened)) [RR: 1.01 (0.92–1.11)]. Although not powered to assess all-cause mortality, the numerical difference in lung cancer death was not preserved in the all-cause mortality statistic. This result has been observed in other cancer screening trials such as the Minnesota Colon Cancer Control Study.[8] It is important to clarify what this result means. A common misconception is that all-cause mortality is unchanged in cancer screening trials because death is inevitable. While it is true we all die, NELSON suggests that when approximately one in 7 individuals has experienced the event of interest, there was no suggestion death is delayed in the screening arm. At the same time, the study lacks power to render a final verdict on this outcome, so residual uncertainty is present.

One notable comparison between the NELSON trial and the NLST is the markedly reduced rate of a positive screening LDCT result in NELSON (2.1% vs 24.2%). This may be explained by what the trials considered as "positive." The

Table 1 Clinical Trials for Lung Cancer Screening with LDCT

Clinical trial (year), country	Comparison/control group	Eligible subjects	Rate of adherence	Rate of positive screening LDCT	Lung cancer incidence	Lung cancer mortality	All-cause mortality
NLST (2011),[1] United States	3 annual screenings with LDCT vs single-view posteroanterior chest radiography	I. 55–74 years II. Male or female III. 30 pack-years IV. Quit within 15 years	>90%	24.2%	645 vs 572 (per 100,000 person-years) (RR: 1.13, [1.03–1.23])	247 vs 309 (RRR:20%, [6.8 to 26.7]; p= 0.004)	6.7% (95% CI, 1.2 to 13.6; p = 0.02)
DANTE (2015),[3] Italy	4 annual screenings with LDCT vs no screening	I. 60–74 years old II. Male smokers or former smokers III. 20 pack-years IV. Quit less than 10 years	N/A	37%	8.23% vs 6.07% (p=−.0418)	543 vs 544 (HR: 0.993; 95% CI, 0.688–1.433) [Not significant]	1655 vs 1742 per 100,000 person-years (HR: 0.947; 95% CI, 0.769–1.165) [Not Significant]
ITALUNG (2017),[4] Italy	4 annual screenings with LDCT vs no screening	I. 55–69 years old II. Male or female III. 20 pack-years IV. Quit less than 10 years	81%	N/A	67 vs 71 ((RR)=0.93; 95% CI 0.67 to 1.30)	30% reduction (RR=0.70; 95% CI 0.47 to 1.03) [Not significant]	17% reduction (RR=0.83; 95% CI 0.67 to 1.03) [Not significant]
LUSI (2019),[5] Germany	5 annual screenings with LDCT vs no screening	I. 50–69 years old II. Male or female III. >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years IV. Quit less than 10 years	>90%	4–22%	85 vs 67 (p=0.16)	HR: 0.74 (95% CI: 0.46–1.19; p = 0.21) [Not significant]	HR = 0.99 [95% CI: 0.79–1.25], p =0.95 [Not significant]
NELSON (2020),[6] Netherlands	4 annual screenings with LDCT vs no screening	I. 50–74 years old II. Male III. >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years IV. Quit less than 10 years	90%	2.1%	5.58 vs 4.91 cases per 1000 person-years	2.50 deaths vs 3.30 deaths per 1000 person-years CR: 0.76 (M) (0.61 to 0.94; P = 0.01)	13.93 vs 13.76 deaths per 1000 person-years, RR: 1.01 (0.92–1.11)

NLST defined LDCT's with any non-calcified nodule measuring at least 4 mm in any diameter as well as radiographic images that revealed any non-calcified nodule or mass as positive. Meanwhile, NELSON classified a non-calcified nodule into 4 different categories based on size or growth pattern. The trial protocol defined nodule category (NODCAT) category IV lesions [solid >500 mm,[6] partial solid with solid component >500 mm[6] and solid, pleural based >10 mm dmin] and growth category (GROWCAT) C lesions to be identified as "positive." In NELSON, another 2069 scans (9.2%) were inconclusive. Thus, the difference in positive screen results may in part be explained by nomenclature.

Finally, the harms of screening with LDCT, mainly the false positive rates and their attendant downstream effects, must be considered. CT screening can lead to multiple diagnostic follow-up procedures, including major thoracic surgical procedures (thoracotomy, video-assisted thoracoscopic surgery [VATS], median sternotomy, or mediastinoscopy) for non-cancer outcomes.[9] This concern has been inadequately addressed in the NELSON trial given no report on the number of PET/CTs, needle biopsies, and VATS was done in each of the study arms for a false positive result. This is vital in the context that real-world data have shown a higher false positive rate compared to the trial cohorts (58.2% real-world vs 26.3% in NLST).[10] The risk of radiation exposure from annual CT scans, albeit low dose, needs to be considered.

Lastly, 46.8% vs 7.1% of the lung cancers detected by screening were Stage I. Some may feel this is evidence of efficacy. Unfortunately, neither stage of diagnosis nor 5-year survival is a suitable metric to assess screening programs, as both are susceptible to lead and lengthen time bias. As such, mortality rates in a randomized population are the sole suitable metric for screening.

In light of prior trials with no significant mortality benefit, and difficulties interpreting NLST due to a non-standard control arm (CXR) and overall survival differences that are not fully accounted for by reductions in lung cancer–specific death, and which were no longer present in extended follow-up and subsequent publication,[2] the NELSON trial provides important clarity for LDCT screening. NELSON failed to show any suggestion of all-cause mortality benefit, and as such we believe further investigation is required to assess the full impact of lung cancer screening. As of 2020, in the process of shared decision-making with patients, we would suggest the following counseling: If you elect to undergo lung cancer screening, there is 13.93% risk of death at 10 years with screening and 13.76% risk of death without, and those percentages are statistically indistinguishable. As for the risk of lung cancer death, it is decreased from 3.2 to 2.4% with screening, a difference of 0.74%. Communication of these facts is essential to informed decision-making.

Corresponding Author: Vinay Prasad, MD, MPH; Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA (e-mail: vinayak.prasad@ucsf.edu).

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