Long-term follow-up results from the DANTE trial of lung cancer screening

Review of: **Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography.**
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Reviewers: Gregory Radin, MD[1] and Katrina Steiling, MD, MSC[1]

[1] The Pulmonary Center; Boston University School of Medicine; Boston, MA

Background/Rationale

Lung cancer remains the leading cause of cancer-related death in both men and women. While the chance for cure is higher in early stage lung cancers, only 16% of lung cancers are diagnosed at an early stage (Stage I - II)(2). Low-dose computerized tomography (LDCT) has been proposed as a screening method for lung cancer, with the goal of detecting early-stage lung cancers in high-risk asymptomatic individuals. The National Lung Screening Trial (NLST) showed a 20% reduction in lung cancer mortality with annual LDCT compared to chest x-ray screening, however replication of this outcome from other trials is currently not available.

Objective

Compare the effectiveness of LDCT over 5 annual scans versus usual care on lung cancer mortality.

Methods

Design: Prospective randomized clinical trial

Setting: Two community hospitals in Milan, Italy

Participants: Men aged 60-74 who were current smokers or former smokers that quit within 10 years and had a cumulative smoking exposure of at least 20 pack-years.

Intervention: A total of 2450 subjects underwent baseline testing which included baseline chest-radiography, and 3-day sputum cytology testing. All enrolled subjects underwent annual re-evaluation, which included interval smoking history, medical history, and physical examination. Subjects randomized to the LDCT arm underwent baseline LDCT of the thorax, and four subsequent annual LDCT screening rounds.

Outcomes: The primary endpoints were lung cancer mortality and all-cause mortality. The secondary endpoints included the incidence of lung cancer, lung cancer stage, and rate of surgical resection.

Main Results

There were significantly more cancers detected in the LDCT screening group compared to control (8.2% vs 6.1%) and a greater proportion of these were stage I cancers (45% vs 22% of cancers identified). Over a median follow up was 8.35 years, LDCT screening did not result in a significant difference in lung cancer mortality (543 per 100,000 person-years in the LDCT group compared to 544 in the control group) or in all-cause mortality (1,655 per 100,000 person-years in LDCT group versus 1,742 in the control group). A stage shift in the cancers diagnosed was not observed with subsequent rounds of screening compared to the initial round.

Conclusion

Lung cancer screening with yearly LDCT in the DANTE trial detected more lung cancers overall and more early stage lung cancers. In contrast to the NLST however, this trial did not show a lung cancer specific or all-cause mortality benefit of LDCT screening compared to annual clinical evaluation. This study was underpowered to detect a mortality difference between the groups.

Commentary

There are several differences between the inclusion criteria and execution of the DANTE trial(1) compared to the NLST(3) which could account for the divergent outcomes of these trials. Perhaps the most significant difference is the exclusion of women in the DANTE trial(1), compared to 41% female participants in the NLST(3). While female participants were equally likely to develop lung cancer as men in the NLST, a post-hoc analysis suggested that women derived a greater mortality benefit from LDCT screening (mortality risk ratio 0.73 in women vs 0.92 in men, $p = 0.08$ for interaction)(3). Another significant difference in the DANTE study population was a higher incidence of overall cancers (8.23%) and screen-detected cancers (5.3%) compared to the NLST (4.03% and 2.47%) and other European lung cancer screening trials, and more than double the rate of adjusted lung cancer mortality in the screening group compared to NLST (543 vs 247 per 100,000 person-years). This result may have been influenced by inclusion of older participants and a more recent maximum smoking quit date, albeit with less minimum cumulative cigarette smoke exposure (1). An analysis of the NLST data showed that the highest-risk quintile of screen-eligible individuals derived the greatest mortality benefit from lung cancer screening(4) however the high incidence of cancer in the study population in DANTE did not translate to a high benefit to screening.

Rates of overdiagnosis and underdiagnosis were higher in the DANTE trial, and this illustrates the importance of integrating standardized evaluation and reporting of screening CT examinations and follow up of abnormal tests in order to maximize the benefit of screening. Up to 18.5% of screen detected cancers in the NLST were overdiagnoses and presumed indolent(5); calculating a similar figure for the DANTE trial yields 48% overdiagnosis of screen-detected cancers, which is similar to the rates seen in two other small European trials(6, 7). Additionally, there was a relatively high proportion of lung cancers missed by LDCT screening examinations in this trial compared to other studies(7–9). Advances in CT technology since the initiation of the DANTE trial and the use of volumetric assessment may improve the sensitivity of screening protocols(10). Second, this study illustrates potential issues related to lung nodule

evaluation even within the context of a randomized clinical trial. Previous studies have shown that adherence to nodule evaluation guidelines are low, with nearly half of patients in a retrospective VA study undergoing evaluation inconsistent with Fleischner Society guidelines(11). In the DANTE trial, definitive diagnosis and treatment of lung cancer was delayed in 19 participants, with progression of disease in 5 of 52 patients with Stage I lung cancer during observation. While this false negative rate is similar to other trials (8-17%)(12–14), this observation highlights the limitations of a single LDCT screening examination to definitively exclude malignancy. In addition, these results underscore the importance of having dedicated radiologists reading screening CT examinations in a standardized manner(15).

Another difference is the study setting, with the NLST being a multi-center study conducted at academic medical centers in the United States(3) while the DANTE trial was conducted at two community hospitals in Italy(1) which could have resulted in differences in evaluation and management of positive findings in the DANTE trial. There were significant differences in the rates of invasive procedures in the DANTE trial, particularly for benign lesions. There was a higher rate of surgical procedures for benign lesions (1.34%) as compared to the NLST (0.96%). The DANTE trial had higher surgical mortality than the NLST (3.3% vs 1%). One potential cause for this difference could be the differences in inclusion criteria and patient factors in this trial compared to the NLST. However, given that this rate of surgical mortality is similar to the figure cited in the US National Cancer Database (3.4%), it may also represent hospital-specific or surgeon-specific factors which were less well specified in the DANTE trial as compared to the NLST, which was performed at specialized cancer care hospitals and academic medical centers. These observations reinforce the need for standardized evidence-based protocols for evaluation of abnormal LDCT screening examinations to minimize both over- and under-evaluation, and focus invasive evaluations and procedures to centers and providers with extensive experience in managing pulmonary nodules and lung cancer.

Despite these limitations, the DANTE trial was a well-conducted study with high rates of adherence to the screening protocol and standardized follow-up. The sample size was much smaller in the DANTE trial compared to the NLST due to an overestimate of the effect size of LDCT on lung cancer detection(1, 3) and was not powered to exclude a benefit to LDCT for lung cancer screening. The results of other larger European Studies LDCT lung cancer screening trials are anticipated in the next year(8, 9), and the DANTE trial can serve to increase the power of a meta-analysis of these trials to definitively evaluate whether a benefit to LDCT screening for lung cancer can be replicated in European populations and outside of academic medical centers.

References

1. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, Brambilla G, Angeli E, Aranzulla G, Chiti A, Scorsetti M, Navarria P, Cavina R, Ciccarelli M, Roncalli M, Destro A, Bottoni E, Voulaz E, Errico V, Ferraroli G, Finocchiaro G, Toschi L, Santoro A, Alloisio M, DANTE Study Group. Long-term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. *Am J Respir Crit Care Med* 2015;doi:10.1164/rccm.201408-1475OC.

2. Cancer of the Lung and Bronchus - SEER Stat Fact Sheets. at <http://seer.cancer.gov/statfacts/html/lungb.html>.

3. The National Lung Screening Trial Research Team. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. *N Engl J Med* 2011;365:395–409.

4. Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, Silvestri GA, Chaturvedi AK, Katki HA. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med* 2013;369:245–254.

5. Patz EF Jr, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemägi MC, Chiles C, Black WC, Aberle DR, for the NLST Overdiagnosis Manuscript Writing Team. Overdiagnosis in Low-Dose Computed Tomography Screening for Lung Cancer. *JAMA Intern Med* 2013;doi:10.1001/jamainternmed.2013.12738.

6. Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, Fabbri A, Galeone C, Negri E, Sozzi G, Pelosi G, La Vecchia C. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP* 2012;21:308–315.

7. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, Døssing M, Hansen H, Kofoed KF, Larsen KR, Mortensen J, Rasmussen JF, Seersholm N, Skov BG, Thorsen H, Tønnesen P, Pedersen JH. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax* 2012;67:296–301.

8. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, van Iersel CA, van den Bergh KAM, van 't Westeinde S, van der Aalst C, Thunnissen E, Xu DM, Wang Y, Zhao Y, Gietema HA, de Hoop B-J, Groen HJM, de Bock GH, van Ooijen P, Weenink C, Verschakelen J, Lammers J-WJ, Timens W, Willebrand D, Vink A, Mali W, de Koning HJ. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009;361:2221–2229.

9. Lopes Pegna A, Picozzi G, Falaschi F, Carrozzi L, Falchini M, Carozzi FM, Pistelli F, Comin C, Deliperi A, Grazzini M, Innocenti F, Maddau C, Vella A, Vaggelli L, Paci E, Mascalchi M, ITALUNG Study Research Group. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer* 2013;8:866–875.

10. Gavrielides MA, Kinnard LM, Myers KJ, Peregoy J, Pritchard WF, Zeng R, Esparza J, Karanian J, Petrick N. A resource for the assessment of lung nodule size estimation methods: database of thoracic CT scans of an anthropomorphic phantom. *Opt Express* 2010;18:15244–15255.

11. Wiener RS, Gould MK, Slatore CG, Fincke BG, Schwartz LM, Woloshin S. Resource Use and Guideline Concordance in Evaluation of Pulmonary Nodules for Cancer: Too Much and Too Little Care. *JAMA Intern Med* 2014;doi:10.1001/jamainternmed.2014.561.

12. Veronesi G, Maisonneuve P, Spaggiari L, Rampinelli C, Pardolesi A, Bertolotti R, Filippi N, Bellomi M. Diagnostic performance of low-dose computed tomography screening for lung cancer over five years. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer* 2014;9:935–939.

13. Xu DM, Yip R, Smith JP, Yankelevitz DF, Henschke CI, I-ELCAP Investigators. Retrospective review of lung cancers diagnosed in annual rounds of CT screening. *AJR Am J Roentgenol* 2014;203:965–972.

14. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers J-WJ, Nackaerts K, Vliegenthart R, ten Haaf K, Yousaf-Khan UA, Heuvelmans MA, Thunnissen E, Oudkerk M, Mali W, de Koning HJ. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol* 2014;15:1342–1350.

15. Mazzone P, Powell CA, Arenberg D, Bach P, Detterbeck F, Gould MK, Jaklitsch MT, Jett J, Naidich D, Vachani A, Wiener RS, Silvestri G. Components necessary for high-quality lung cancer screening: American College of Chest Physicians and American Thoracic Society Policy Statement. *Chest* 2015;147:295–303.