Editorial Commentary

Optimal lung cancer screening intervals following a negative low-dose computed tomography result

Monica E. Reyes[1], Matthew B. Schabath[1,2]

[1]Department of Cancer Epidemiology, [2]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Correspondence to: Matthew B. Schabath, PhD. H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive MRC-CANCONT, Tampa, FL 33612, USA. Email: Matthew.Schabath@Moffitt.org.

Provenance: This is an invited article commissioned by the Section Editor Jun Zhou (Department of Nuclear Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

Comment on: Robbins HA, Berg CD, Cheung LC, *et al.* Identification of candidates for longer lung cancer screening intervals following a negative low-dose computed tomography result. J Natl Cancer Inst 2019;111:996-9.

Submitted Jul 30, 2019. Accepted for publication Aug 16, 2019.

doi: 10.21037/jtd.2019.08.85

View this article at: http://dx.doi.org/10.21037/jtd.2019.08.85

For the last several decades lung cancer has been the most commonly diagnosed cancer worldwide with an estimated 2.1 million new lung cancer diagnoses in 2018 and accounting for 12% of the global cancer burden (1). Lung cancer is the leading cause of cancer-related death in the United States and the five-year survival rate for non-small cell lung cancer and small cell lung cancer combined is a dismal 19% (2). The high mortality rates and poor survival outcomes of this disease are primarily attributed to the majority of patients diagnosed with late stage disease, when the prospects for cure are limited. However, local therapy for lung cancers diagnosed at early stage is associated with significantly improved overall survival which highlights a critical need for identifying early-stage lung cancers. In 2011, results of the U.S. National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality for individuals screened by low-dose helical computed tomography (LDCT) compared to standard chest radiography among high-risk current and former smokers (3). Following the publication of the NLST results, recommendations for annual CT screens for eligible high-risk individuals were issued by the U.S. Preventive Services Task Force (4) and Centers for Medicare and Medicaid Services (CMS) (5).

Despite the conclusive benefits shown by the NLST, there are noted limitations and concerns associated with lung cancer screening by LDCT including high rates of false-positives and indeterminate pulmonary nodules of which only a fraction actually develop into cancer. Another unanswered question is the optimal frequency of LDCT screening, especially among screen-negative individuals since studies have reported a significant reduction in lung cancer incidence among NLST participants with a baseline negative screen compared to those with a baseline positive screen (6,7). Increasing the time between screening intervals among individuals at lowest risk of lung cancer could mitigate potential harms associated with lung cancer screening including false-positives and radiation-induced cancers. As such, Robbins *et al.* (8) analyzed 23,328 participants in the NLST who had a negative LDCT screen, defined as the absence of any nodules ≥4 mm in longest diameter, to develop an individualized model for lung cancer risk after a negative-screen. They sought to build on their previously developed Lung Cancer Risk Assessment Tool (LCRAT) (9) to develop a new model that predicts short-term lung cancer risk following a negative CT screen. Using conventional lung cancer risk factors and the LCRAT, the authors calculated individual one-year baseline "prescreening risk" and then included the most informative radiological CT findings (LCRAT + CT) that influence the relationship between prescreening risk and future lung cancer risk. The CT features included eleven radiological ("semantic") features that are included in the NLST dataset (e.g., CT-detected emphysema, consolidation, and pleural thickening or effusion). Using their newly developed LCRAT + CT model, the authors report that among the ~70% of screen-negatives that did not

have emphysema nor consolidation, their lung cancer risk at the next screening interval was reduced from 0.3% median risk (prescreening risk) to 0.2% median risk (risk at next screen). Among the ~30% screen-negatives that had CT-detected emphysema, lung cancer risk increased ~1.6-fold (0.3% median prescreening risk to 0.5% median risk at next screen); among the 0.6% of screen-negatives with consolidation, lung cancer risk increased ~5-fold (0.3% median prescreening risk to 1.6% median risk at next screen). The authors also examined potential risk thresholds to identify participants for longer screening intervals. In a scenario using a threshold of 0.3% next-screen lung cancer risk, 57.8% of screen-negatives (N=20,522) were below this threshold of which 33 of the 138 next-screen lung cancers were detected (23.9%) and 1,464 of the 2,937 next-screen false-positives occurred (49.8%). This finding suggests that if the screening interval were increased for these 57.8% screen-negatives, diagnosis would have been delayed for about 24% of the lung cancers but ~50% false-positives could have been avoided among the screen-negatives.

Certainly, the authors do acknowledge some limitations including lack of external validation, lack of comparisons with other prescreening risk models, they could not provide specific length for longer intervals since the NLST used annual screening intervals, and the absence of an estimated reduction of screening effectiveness from lengthening intervals. There are other potential limitations, not noted by the authors, including use of the radiological features in the NLST dataset of which their validity are indeterminate. It's not evident if the radiologists in the NLST were trained to report these abnormalities and nonspecific findings in a uniform and standardized way. As such, the variability, accuracy, and completeness of these specific data elements are unknown because a systematic review of these CT images with standardized reporting would be necessary. However, a nested case-control study (10) of the NLST utilized radiologists to extract semantic radiologic features from negative screens with small pulmonary nodules and identified a model with 5 features that yielded a receiver operating characteristic curve of 0.932 to predict cancer risk. Of particular note, results from the nested case-control study (10) found that one of the most informative features was emphysema which was also found in the LCRAT+CT model. Clearly, the utility of image-based features for biomarkers to predict lung cancer risk is certainly of merit (11). Another potential limitation are the significant differences in overall and progression-free survival among screen-detected (incident) lung cancers depending upon whether the antecedent screens were negative or positive prior to the screen of the cancer diagnosis (7). Specifically, although there were fewer screen-detected lung cancers with negative screens at earlier time points, these individuals had significantly lower survival outcomes than those with positive antecedent screens. These results imply that screen-detected lung cancers following previous negative screens are a more aggressive phenotype despite having a lower cancer risk and lower incidence of lung cancer. Further studies that balance cancer risk and survival outcomes will likely be necessary to determine optimal screening intervals and frequency. Additionally, risk-benefit analyses should be conducted prior to this, or any, decision tool is implemented clinically.

Overall, the LCRAT + CT model demonstrates the potential utility in reducing harm associated with frequent CT screening (i.e., false-positives, increased cancer risk) while maintaining efficacy of early detection by LDCT. As it is imperative that other datasets be utilized to validate these results, recent lung cancer screening randomized trials having been published: the Multicentric Italian Lung Detection (MILD) trial (12) and the German Lung Cancer Screening Intervention (LUSI) trial (13). Additionally, since the publication of the NLST results (3), the implementation and evolution of lung cancer screening guidelines (14,15) have improved nodule management in the lung cancer screening setting. Thus, *post hoc* analyses conducted in the NLST may not necessarily reflect what is occurring in more recent clinical trials and in the "real world setting". In fact, the MILD trial reduced unnecessary surgery through active surveillance of subsolid lesions and selective use of PET imaging which improved differential diagnosis, especially when compared to the NLST [4.5% surgical resection rate for benign histology versus 24.4% in the NLST (3)]. Thus, with the emergence of the MILD (12) and LUSI trials (13), and anticipated publication of the results of the NELSON trial (16), risk models and decision tools that were based solely on data from the NLST will likely need to be reassessed in these newer clinical trials. The thoughtful approach presented by Robbins *et al.* (8) provide the framework for future *post hoc* analyses to determine optimal screening frequencies especially among patients with initially negative screens.

Acknowledgments

Funding: ME Reyes was supported by Moffitt's postdoctoral training program in molecular epidemiology (5T32CA147832-09). MB Schabath was funded in part

by the National Institutes of Health (NIH) grant U01 CA200464.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
4. Moyer VA, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160:330-8.
5. Centers for Medicare and Medicaid Services. Decision memo for screening for lung cancer with low-dose computed tomography (LDCT) (CAG-00439N). 2019. Available online: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274
6. Patz EF Jr, Greco E, Gatsonis C, et al. Lung cancer incidence and mortality in National Lung Screening Trial participants who underwent low-dose CT prevalence screening: a retrospective cohort analysis of a randomised, multicentre, diagnostic screening trial. Lancet Oncol 2016;17:590-9.
7. Schabath MB, Massion PP, Thompson ZJ, et al. Differences in Patient Outcomes of Prevalence, Interval, and Screen-Detected Lung Cancers in the CT Arm of the National Lung Screening Trial. PLoS One 2016;11:e0159880.
8. Robbins HA, Berg CD, Cheung LC, et al. Identification of candidates for longer lung cancer screening intervals following a negative low-dose computed tomography result. J Natl Cancer Inst 2019;111:996-9.
9. Katki HA, Kovalchik SA, Berg CD, et al. Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. JAMA 2016;315:2300-11.
10. Liu Y, Wang H, Li Q, et al. Radiologic Features of Small Pulmonary Nodules and Lung Cancer Risk in the National Lung Screening Trial: A Nested Case-Control Study. Radiology 2018;286:298-306.
11. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology 2016;278:563-77.
12. Pastorino U, Silva M, Sestini S, et al. Prolonged Lung Cancer Screening Reduced 10-year Mortality in the MILD Trial. Ann Oncol 2019. [Epub ahead of print].
13. Becker N, Motsch E, Trotter A, et al. Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. Int J Cancer 2019. [Epub ahead of print].
14. Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16:412-41.
15. American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADS). Available online: https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads. Accessed July 29, 2019.
16. De Koning H, Van der Aalst C, Ten Haaf K, et al. Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. J Thorac Oncol 2018;13:S185.

Cite this article as: Reyes ME, Schabath MB. Optimal lung cancer screening intervals following a negative low-dose computed tomography result. J Thorac Dis 2019;11(Suppl 15):S1916-S1918. doi: 10.21037/jtd.2019.08.85

