Editorial

Lung cancer screening: not all nodules are created equal

Gaurav Shukla[1], Noelle L. Williams[1], Christopher Luminais[2], Bo Lu[1], Wenyin Shi[1]

[1]Department of Radiation Oncology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA 19107, USA; [2]Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA 19107, USA

Correspondence to: Wenyin Shi, MD, PhD. Sidney Kimmel Medical College at Thomas Jefferson University, 111 South 11th St., Philadelphia, PA 19107, USA. Email: Wenyin.Shi@Jefferson.edu.

Submitted Aug 29, 2016. Accepted for publication Aug 31, 2016.
doi: 10.21037/jtd.2016.10.17
View this article at: http://dx.doi.org/10.21037/jtd.2016.10.17

The incidence and mortality from bronchogenic malignancies continue to be high, with an estimated 224,000 new cases and an estimated 158,000 deaths in the United States in 2016 (1). Approximately 75% of patients present with locally advanced disease or metastatic disease, usually beyond the scope of curative therapies (2). This has prompted the development of screening programs which utilize low-dose chest computed tomography (CT) imaging in asymptomatic high-risk individuals. The NELSON trial is a Dutch/Belgian screening trial randomizing high-risk patients (as determined by smoking history and age) to receive either no screening or a series of low-dose chest CT imaging studies at prespecified time-points (year 1, 2, 4, and 6). Patients with suspicious nodules found on the screening CT imaging were subsequently evaluated with repeat imaging, biopsy, or other appropriate interventions (3). Over 15,000 patients have been accrued; the investigators hypothesized that screening will decrease 10-year lung cancer mortality by at least 25% (3). While the primary outcome data continue to mature, the available information on over 7,500 patients with serial CT imaging lends itself to preliminary analysis.

We read with great interest the recent publication by Walter and colleagues (4) identifying a distinct subset of patients accrued to the NELSON trial. The authors found that a subgroup of patients developed new solid nodules on the second and third screening exams. Analysis of these "interval" nodules shows that the risk of finding cancer in them was statistically higher than the risk of malignancy in nodules found at baseline. In a previous report in 2014, it showed the nodule volume could be used for risk stratification (5). However, the current study suggested the risk-stratification cutoff points for interval nodules are quite different than those for nodules found at baseline. This finding meshes with the theory that nodules arising in the relatively short interval between screening exams are more likely to be growing more rapidly—and thus, are more likely to represent malignancy—than nodules found on the baseline exam.

The implication of this analysis is that "interval nodules" represent a distinct entity from "baseline nodules," and that separate criteria for their evaluation and management should be developed. We strongly agree with this assertion, and commend the authors for demonstrating with data a concept that intuitively makes sense. We further commend the authors and the trial designers for making use of semi-automated volumetric assessment methods, which improved the precision of diameter and volume measurements (6). Image analysis techniques are of particular importance with lung nodules. Early analysis of the NELSON data compared a computer-aided detection (CAD) algorithm against gold-standard expert radiologists, and found that the CAD technique increased sensitivity of nodule detection from 78.1% to 96.7% (7). Machine learning algorithms and sophisticated image feature extraction methods have already been shown to have predictive and prognostic utility in the analysis of cancerous lung nodules [e.g., assessing risk of distant metastasis (8) and response to therapy (9)]. It stands to reason that using such algorithms to characterize nodules found on screening studies may further improve the risk stratification, allowing clinicians to better choose the patients in whom more aggressive follow-up is warranted as compared to conservative management. Indeed, radiomic analysis of interval nodules has the potential to reveal a "feature signature" that predicts a positive biopsy with more discriminatory power than volume measurements alone. Such a feature set may allow better stratification of nodules found on baseline studies as well.

Another finding worth noting is that a substantial portion of patients found to have developed interval cancers were beyond Stage I. This may certainly represent the aggressiveness of some fast growing cancers. However, the obvious increase of patients beyond Stage I in the third screening round as compared to second screening round raised the question of optimal frequency of screening CTs. In the American National Lung Screening Trial (NLST), patients received three annual CT scans; as compared to in the NELSON trial, the intervals between exams could be as high as 2.5 years. The American study, published in 2011, demonstrated a 20% relative reduction in lung cancer specific mortality, as well as a 6.7% relative reduction in all-cause mortality (10), leading to a new recommendation that all high-risk individuals should be offered low-dose CT screening under the annual imaging schedule described in the protocol (11). However, the staging information of patients diagnosed with each annual screening CT was not reported. A recent retrospective analysis of the NLST data did show that patients with initial negative screening exams were less likely to develop lung cancer or experience lung-cancer-specific mortality as compared to all patients in the study, and that the yield of lung cancer in subsequent interval nodules was also relatively low (12). The population of patients still needs to be better defined, in whom longer intervals between screening CTs are appropriate. While we recognize that balancing the cost-effectiveness of screening carries great importance, we must remember the primary goal of these screening studies. With subsequent screening identifying an increasing portion of patients with advanced disease, the imaging interval may need to be adjusted.

Nevertheless, these findings clearly warrant the establishment of more stringent guidelines for the management of new solid nodules ("interval nodules") found after the baseline study during low-dose CT screening. We support the use of volumetric measurements, and would advocate for the incorporation of more sophisticated radiomic techniques as they become more clinically validated. To our knowledge, such a study of interval nodules has not been performed in the UKLS or NLST cohorts; those datasets would likely provide further insight for the development of more stringent guidelines. We eagerly await the primary outcome data for the NELSON and other European trials to help clarify the questions around lung cancer screening.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Long Jiang (Second Affiliated Hospital, Institute of Respiratory Diseases, Zhejiang University School of Medicine, Hangzhou, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Walter JE, Heuvelmans MA, de Jong PA, *et al.* Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncol 2016;17:907-16.

References

1. Siegel RL, Miller KD, Jemal A, et al. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Molina JR, Adjei AA, Jett JR. Advances in chemotherapy of non-small cell lung cancer. Chest 2006;130:1211-9.
3. Ru Zhao Y, Xie X, de Koning HJ, et al. NELSON lung cancer screening study. Cancer Imaging 2011;11 Spec No A:S79-84.
4. Walter JE, Heuvelmans MA, de Jong PA, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncol 2016;17:907-16.
5. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol 2014;15:1332-41.
6. Revel MP, Bissery A, Bienvenu M, et al. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology 2004;231:453-8.
7. Zhao Y, de Bock GH, Vliegenthart R, et al. Performance of computer-aided detection of pulmonary nodules in low-dose CT: comparison with double reading by nodule volume. Eur Radiol 2012;22:2076-84.
8. Coroller TP, Grossmann P, Hou Y, et al. CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. Radiother Oncol 2015;114:345-50.
9. Huynh E, Coroller TP, Narayan V, et al. CT-based radiomic analysis of stereotactic body radiation therapy patients with lung cancer. Radiother Oncol 2016;120:258-66.
10. 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.
11. 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.
12. 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.

Cite this article as: Shukla G, Williams NL, Luminais C, Lu B, Shi W. Lung cancer screening: not all nodules are created equal. J Thorac Dis 2016;8(10):E1257-E1259. doi: 10.21037/jtd.2016.10.17