Commentary

The bell tolls for indeterminant lung nodules: computer-aided nodule assessment and risk yield (CANARY) has the wrong tune

David O. Wilson[1], Jiantao Pu[2]

[1]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, [2]Departments of Radiology and Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence to: David O. Wilson, MD, MPH. Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA. Email: wilsondo@upmc.edu; Jiantao Pu, PhD. Department of Radiology, University of Pittsburgh, Pittsburgh, PA, USA. Email: puj@upmc.edu.

Submitted Jun 07, 2016. Accepted for publication Jun 21, 2016.
doi: 10.21037/jtd.2016.07.85
View this article at: http://dx.doi.org/10.21037/jtd.2016.07.85

There is a potential epidemic of indeterminant pulmonary nodules (IPN) with the evolution of low dose computed tomography (LDCT) screening programs for lung cancer. The National Lung Screening Trial (NLST) demonstrated that annual screening with LDCT reduces mortality from lung cancer by 20% in high risk individuals. However, 39% of all participants and 24% of all screening LDCTs were interpreted as showing a positive result, and the false positive rate was >96% (1). Thus, the large majority of LDCT detected lung nodules are not lung cancer. Unfortunately, the current predictive tools to discriminate benign from malignant lung nodules are not reliable, relying on size, location, appearance and growth. Biomarkers are not yet ready for clinical use, such that a large number of follow-up CT and PET scans, invasive biopsies of questionable indication, anxiety and expense are associated with the evaluation of these lung nodules. In this context, differentiating the relatively small number of lung cancers from benign IPNs represents a critically important problem in lung cancer screening and early detection. With this background, Maldonado and colleagues at the Mayo Clinic (2-4) have adapted the computer-aided lung informatics for pathology evaluation and rating (CALIPER) CT based imaging analysis tool developed at Mayo originally for pulmonary fibrosis and other diffuse lung diseases to focus on lung nodules of the adenocarcinoma spectrum only. It is a bit peculiar that the focus would be on noninvasive radiologic—pathologic correlation of pulmonary nodules on the adenocarcinoma spectrum, rather than the more clinically important problem of differentiating benign from malignant nodules. In three articles published in 2014, the Mayo group demonstrated that the computer-aided nodule assessment and risk yield (CANARY) tool could non-invasively risk stratify lung adenocarcinoma into aggressive (invasive adenocarcinoma) and indolent (adenocarcinoma *in situ* and minimally invasive adenocarcinoma). While this is an important question, it pales in significance to determining benign *vs.* malignant nodules, and reducing the false positive LDCT rate. This perspective will review the CANARY technology relative to LDCT lung screening and the current universe of IPNs.

On the technical side, CANARY relies on three procedures: (I) lung parenchymal segmentation and classification; (II) nodule extraction and (III) nodule characterization. Many technical details are not presented. For example, lung parenchyma is classified into five types: normal, emphysema, reticular, ground glass and honeycomb. The performance of this classification is not referenced to a gold standard nor described in any detail. In terms of nodule extraction, the proximity of lung cancers to blood vessels has the potential to confound the region-growing approach used to segment the nodules. Specifically, the use of a seed voxel relies on only 26 connected voxels, with any changes in the location of the seed voxel having a major impact on the later ROI development. Finally, the process of "arbitrarily selecting 774 ROI (size 9×9 voxels) spanning the radiographic spectrum of the lesions …" is potentially flawed because of confounding a three dimensional concept (voxel) into a two dimensional ROI. For example, a CT scan with slice thickness of 5 mm will give different classification results than a CT scan with 2.5 mm slice thickness. In addition, the size of the image voxels will vary across different body sizes,

which needs to be taken into account.

On the clinical side, indolent, potentially inconsequential lung cancer is a relatively new concept, owing to two factors. First, lung cancer has a high case fatality rate such that the idea of clinically inconsequential lung cancers never had much traction in the clinic. Second, lung cancer screening was nonexistent until the recent advent of LDCT as a research tool in the early 2000s, so these tumors were rarely identified . In the past decade, there have been several studies that have looked at this problem, including our own published study of indolent lung cancers in the Pittsburgh Lung Screening Study (PLuSS) (5). The range of indolent, clinically insignificant screen detected lung cancers in these studies is 10–20%, a much lesser problem than differentiating benign from malignant IPNs. While the CANARY system may represent a novel noninvasive tool for the accurate and reproducible risk stratification of lung adenocarcinoma nodules, it does not help with the larger, more clinically important question of benign *vs.* malignant lung nodules. In addition, the authors utilized post treatment progression free survival as a surrogate for the biological behavior of lung adenocarcinoma, which is purely speculative.

In conclusion, CANARY offers a novel noninvasive way to risk stratify lung adenocarcinomas, using advanced imaging software and methodology. It does not address the more clinically important problem of differentiating benign *vs.* malignant IPNs. It also does not take into account the very real problem that within the adenocarcinoma spectrum, the biological behavior of indolent cancers is dynamic and often unpredictable. Thus, while CANARY is novel, the overall significance is limited by virtue of its rather narrow applicability.

Acknowledgements

Funding: This study was supported by the University of Pittsburgh Cancer Institute's Specialized Program of Research Excellence (SPORE) in Lung Cancer (NCI P50-CA90440), the Cancer Center Core Grant (NCI 2P30 CA047904), NCI R21CA197493, and R01HL096613.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Chen Chen (The Second Xiangya Hospital of Central South University, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Maldonado F, Boland JM, Raghunath S, *et al.* Noninvasive characterization of the histopathologic features of pulmonary nodules of the lung adenocarcinoma spectrum using computer-aided nodule assessment and risk yield (CANARY)--a pilot study. J Thorac Oncol 2013;8:452-60.
Raghunath S, Maldonado F, Rajagopalan S, *et al.* Noninvasive risk stratification of lung adenocarcinoma using quantitative computed tomography. J Thorac Oncol 2014;9:1698-703.
Maldonado F, Duan F, Raghunath SM, *et al.* Noninvasive Computed Tomography-based Risk Stratification of Lung Adenocarcinomas in the National Lung Screening Trial. Am J Respir Crit Care Med 2015;192:737-44.

References

1. 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.
2. Maldonado F, Boland JM, Raghunath S, et al. Noninvasive characterization of the histopathologic features of pulmonary nodules of the lung adenocarcinoma spectrum using computer-aided nodule assessment and risk yield (CANARY)--a pilot study. J Thorac Oncol 2013;8:452-60.
3. Raghunath S, Maldonado F, Rajagopalan S, et al. Noninvasive risk stratification of lung adenocarcinoma using quantitative computed tomography. J Thorac Oncol 2014;9:1698-703.
4. Maldonado F, Duan F, Raghunath SM, et al. Noninvasive Computed Tomography-based Risk Stratification of Lung Adenocarcinomas in the National Lung Screening Trial. Am J Respir Crit Care Med 2015;192:737-44.
5. Thalanayar PM, Altintas N, Weissfeld JL, et al. Indolent, Potentially Inconsequential Lung Cancers in the Pittsburgh Lung Screening Study. Ann Am Thorac Soc 2015;12:1193-6.

Cite this article as: Wilson DO, Pu J. The bell tolls for indeterminant lung nodules: computer-aided nodule assessment and risk yield (CANARY) has the wrong tune. J Thorac Dis 2016;8(8):E836-E837. doi: 10.21037/jtd.2016.07.85

