Autofluorescence bronchoscopy for lung cancer screening: a time to reflect

Oleg Epelbaum[1], Wilbert S. Aronow[1,2]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, [2]Division of Cardiology, Department of Medicine, Westchester Medical Center/New York Medical College, Valhalla, NY, USA

Correspondence to: Wilbert S. Aronow, MD, FCCP, FACP, FACC, FAHA, Professor of Medicine. Cardiology and Pulmonary Divisions, Westchester Medical Center/New York Medical College, Macy Pavilion, Room 141, Valhalla, NY 10595, USA. Email: wsaronow@aol.com.

Submitted May 31, 2016. Accepted for publication Jun 01, 2016.
doi: 10.21037/atm.2016.06.34
View this article at: http://dx.doi.org/10.21037/atm.2016.06.34

The National Lung Cancer Screening Trial (NLCST), which showed a 20% relative risk reduction in lung cancer mortality with screening by low-dose computed tomography (CT) versus plain radiography, has resulted in growing organizational and institutional adoption of this practice across the United States and Canada (1,2). The rationale behind screening for this deadly malignancy with CT is analogous to mammographic screening for breast cancer in that it entails radiological detection of cancer that has already occurred but that is still at an early enough stage such that surgical cure is a possibility. The majority of parenchymal lesions thus detected are adenocarcinomas, which are known for their predilection for the lung periphery and represent the commonest lung cancer histology in North America (3). Chest CT is currently incapable of identifying dysplastic bronchial epithelium and carcinoma in-situ (CIS) prior to conversion to invasive carcinoma—almost all squamous—unlike, for example, the ability of CT colonography to pick up precancerous colonic polyps. The recognition of these pre-invasive bronchial lesions (PBL) has thus far been predicated on direct bronchoscopic inspection and sampling much the same way that abnormal gastroesophageal or cervical mucosa is visualized and biopsied by esophagogastroduodenoscopy or colposcopy, respectively. The limitations of conventional white-light bronchoscopy (WLB) in identifying PBLs have led to long-standing interest in complementary bronchoscopic technologies suitable for this purpose. One such modality is autofluorescence bronchoscopy (AFB), which relies on differences in the wavelength of emitted visible light between normal and diseased mucosa, namely the weaker green autofluorescence exhibited by the latter (4). Analysis of pooled data from the available heterogeneous studies of adding AFB to WLB revealed that the combination has twice the relative sensitivity compared to WLB alone at the expense of a significant reduction in relative specificity (5).

In the April 2016 issue of the journal *Chest*, Tremblay *et al*. report the results of a robustly powered component of the previously published Pan-Canadian Early Detection of Lung Cancer Study wherein 1,300 participants across seven centers underwent screening by AFB in addition to low-dose CT (6). The majority of this at-risk population consisted of active smokers with heavy tobacco exposure, yet only half had evidence of obstructive airways disease, and the mean FEV_1% predicted was normal. Those proceduralists naïve to AFB were mentored or precepted by some of the most experienced AFB operators in the world. Cases performed by the newly trained bronchoscopists were externally audited for quality in the initial stage of the study. This independent review did flag 15 technically suboptimal procedures, and the percentage of patients biopsied varied substantially among study sites. A total of 56 lung cancers were detected by LDCT (4.3%), a prevalence similar to that reported in the NLCST, while AFB identified pathologic findings in 69 subjects, just 5 of whom turned out to have cancer. Moreover, in only 2 of these patients was the lesion missed by LDCT: a case of CIS and a typical carcinoid tumor of unreported size—the latter being a neoplasm that is often quite apparent bronchoscopically without AF—for an overall rate of 0.15% for the bronchoscopic detection of cancer. As a corollary, an AF airway inspection did not pick up a single case of LDCT-occult invasive non-small cell lung cancer. Mild and moderate dysplasia comprised the vast

majority of abnormalities identified by AFB. The authors justifiably concluded that AFB should not be incorporated into current LDCT-based screening algorithms.

What might account for the resounding failure of AFB to enhance CT screening in a trial built upon promising, albeit considerably smaller, prior screening investigations likewise centered in Canada and reporting similar prevalent cancer rates (7,8)? One factor also alluded to by the authors is patient selection: Tremblay *et al*. enrolled subjects theoretically at risk for lung cancer based on a prediction model, whereas in the two preceding studies by McWilliams *et al*. either all or the majority of participants had atypia on automated quantitative cytometry (AQC) of sputum, a technique employed to detect endoluminal shedding of abnormal airway epithelium by squamous cell carcinoma (SqCC) precursors. Broadly, even as the more recent study by McWilliams *et al*. was being published in 2006, the incidence of SqCC relative to adenocarcinoma was decreasing in North America; this trend has continued and presumably also extends to SqCC precursors, namely PBLs (9). The incremental benefit of AFB would be expected to decline in parallel with the shrinking prevalence of its target lesions (5). In this climate, AFB, especially in the hands of inexperienced operators, could be insufficiently sensitive, a problem that may be rectifiable by advances in newer detection techniques such as narrow-band imaging and optical coherence tomography (10,11). Irrespective of the modality used to screen for PBLs, enriching the target population for greater a priori risk of bronchial cytopathic changes ought to provide a more substantial benefit beyond LDCT. Besides sputum AQC, an intriguing candidate might be an airway scraping subjected to gene expression analysis in a manner analogous to that applied successfully by Silvestri *et al*. for the classification of lung nodules and masses (12). In this regard, perhaps bronchoscopic screening for PBLs should be viewed less like the approach to colonoscopic screening, which is protocolized based on clinically determined risk, and more like colposcopy for cervical cancer wherein candidates for mucosal sampling are chosen selectively based on the cytology of preceding Papanicolau smears. It should be noted parenthetically, in defense of AFB, that agreement among pathologists reviewing AFB-guided airway biopsies for dysplasia has been shown to be poor, and in one small study potentially oncogenic chromosomal derangements were found in over 80% of specimens deemed histologically normal (13,14). It has also been proposed that the biopsy process itself may distort the cellular architecture of these tiny lesions.

Viewing the issue of PBLs more globally invites consideration of their natural history since Tremblay *et al*. did find 64 instances of dysplasia thanks to a screening airway examination, which arguably is in fact the main purpose of AFB. Several studies have cast doubt on the linearity of progression from milder to more severe dysplasia then to CIS and finally on to invasive carcinoma (15,16). In another parallel with cervical intraepithelial neoplasia, even severe dysplasia of the bronchial epithelium has been observed to regress spontaneously in over 50% of lesions followed longitudinally (17,18). Progression of lower-grade histology to invasion is exceedingly rare. On a cautionary note, a recent Dutch PBL surveillance study demonstrated that increasing PBL histological grade correlated with the risk of subsequent development of invasive lung cancer, but more of these cancers arose elsewhere in the lungs than at the PBL site (19). Taken together, credible data lend support to the so-called "field carcinogenesis" theory of toxin-induced malignancy and question the clinical implications of finding and addressing a specific PBL as such. Furthermore, unlike detection of early-stage parenchymal lung neoplasia as in the NLCST, or—to continue the analogy—screening for cervical cancer, there is no existing evidence to indicate that identification and elimination of precancerous bronchial mucosa translates into a survival benefit (20).

Tremblay *et al*. should be commended for an ambitious investigation of the impact of AFB on lung cancer screening. The thought-provoking questions raised by their work, which outnumber the questions answered, should provide the impetus for methodological refinement in the study of bronchoscopy as a screening tool in the era of LDCT.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Tremblay A, Taghizadeh N, McWilliams AM,

et al. Low prevalence of high grade lesions detected with autofluorescence bronchoscopy in the setting of lung cancer screening in the Pan-Canadian Lung Cancer Screening Study. Chest 2016. [Epub ahead of print].

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. Canadian Task Force on Preventive Health Care. Recommendations on screening for lung cancer. CMAJ 2016;188:425-32.
3. Lewis DR, Check DP, Caporaso NE, et al. US lung cancer trends by histologic type. Cancer 2014;120:2883-92.
4. Hung J, Lam S, LeRiche JC, et al. Autofluorescence of normal and malignant bronchial tissue. Lasers Surg Med 1991;11:99-105.
5. Sun J, Garfield DH, Lam B, et al. The value of autofluorescence bronchoscopy combined with white light bronchoscopy compared with white light alone in the diagnosis of intraepithelial neoplasia and invasive lung cancer: a meta-analysis. J Thorac Oncol 2011;6:1336-44.
6. Tremblay A, Taghizadeh N, McWilliams AM, et al. Low prevalence of high grade lesions detected with autofluorescence bronchoscopy in the setting of lung cancer screening in the Pan-Canadian Lung Cancer Screening Study. Chest 2016. [Epub ahead of print].
7. McWilliams A, Mayo J, MacDonald S, et al. Lung cancer screening: a different paradigm. Am J Respir Crit Care Med 2003;168:1167-73.
8. McWilliams AM, Mayo JR, Ahn MI, et al. Lung cancer screening using multi-slice thin-section computed tomography and autofluorescence bronchoscopy. J Thorac Oncol 2006;1:61-8.
9. Houston KA, Henley SJ, Li J, et al. Patterns in lung cancer incidence rates and trends by histologic type in the United States, 2004-2009. Lung Cancer 2014;86:22-8.
10. Vincent BD, Fraig M, Silvestri GA. A pilot study of narrow-band imaging compared to white light bronchoscopy for evaluation of normal airways and premalignant and malignant airways disease. Chest 2007;131:1794-9.
11. Lam S, Standish B, Baldwin C, et al. In vivo optical coherence tomography imaging of preinvasive bronchial lesions. Clin Cancer Res 2008;14:2006-11.
12. Silvestri GA, Vachani A, Whitney D, et al. A bronchial genomic classifier for the diagnostic evaluation of lung cancer. N Engl J Med 2015;373:243-51.
13. Venmans BJ, van der Linden JC, Elbers HR, et al. Observer variability in histopathologic reporting of bronchial biopsy specimens: influence on the results of autofluorescence bronchoscopy in detection of preinvasive bronchial neoplasia. J Bronchol 2000;7:210-14.
14. Helfritzsch H, Junker K, Bartel M, et al. Differentiation of positive autofluorescence bronchoscopy findings by comparative genomic hybridization. Oncol Rep 2002;9:697-701.
15. Breuer RH, Pasic A, Smit EF, et al. The natural course of preneoplastic lesions in bronchial epithelium. Clin Cancer Res 2005;11:537-43.
16. Ishizumi T, McWilliams A, MacAulay C, et al. Natural history of bronchial preinvasive lesions. Cancer Metastasis Rev 2010;29:5-14.
17. Bansal N, Wright JD, Cohen CJ, et al. Natural history of established low grade cervical intraepithelial (CIN 1) lesions. Anticancer Res 2008;28:1763-6.
18. Banerjee AK. Preinvasive lesions of the bronchus. J Thorac Oncol 2009;4:545-51.
19. van Boerdonk RA, Smesseim I, Heideman DA, et al. Close surveillance with long-term follow-up of subjects with preinvasive endobronchial lesions. Am J Respir Crit Care Med 2015;192:1483-9.
20. Peirson L, Fitzpatrick-Lewis D, Ciliska D, et al. Screening for cervical cancer: a systematic review and meta-analysis. Syst Rev 2013;2:35.

Cite this article as: Epelbaum O, Aronow WS. Autofluorescence bronchoscopy for lung cancer screening: a time to reflect. Ann Transl Med 2016;4(16):311. doi: 10.21037/atm.2016.06.34

