Lung cancer screening: the path forward

Although the primary results of the National Lung Screening Trial (NLST) were published only 7 years ago, lung cancer screening today is rapidly advancing (1). In this issue of *Translational Lung Cancer Research* (*TLCR*) dedicated to CT screening for lung cancer, we include reviews of many of those advances—some already in clinical use, and some still in development.

We open this issue with a review by de Groot *et al.* of global trends in the epidemiology of lung cancer, including smoking rates, indoor air pollution and occupational exposures, the history and carcinogenesis of tobacco smoking, as well as environmental and genetic risk factors for lung cancer (2). Dr. Pinsky provides us with a world-wide perspective on lung cancer incidence and mortality, a review of randomized controlled trials and demonstration projects of low-dose CT screening for lung cancer, and a summary of screening guidelines and position papers from various countries (3).

Selecting the appropriate population for screening is arguably the most urgent issue in screening. Eligibility criteria for screening have been primarily based on age and smoking history (e.g., NLST criteria ages 55–74, current or former smoker with at least 30 pack-year smoking history, quit date in former smokers within the last 15 years). We know, however, that these criteria will include individuals who are at relatively low risk of developing lung cancer, but will also fail to include a significant proportion of lung cancers (4). Pinsky and Berg suggest that only 26.7% of incident lung cancers would be captured using the original NLST eligibility criteria (5). The challenge is not only to reduce the risks of LDCT screening in patients who are unlikely to die from lung cancer, but also to increase the detection of early stage lung cancer in those at highest risk. As you will see in this issue of *TLCR*, refining screening eligibility criteria on the basis of additional patient characteristics, medical history, family history, and the presence of COPD/emphysema can select a higher risk population and reduce the potential harms of screening in a lower risk population.

Comorbid medical conditions are a confounding issue in patient selection. A patient who meets eligibility criteria may be more likely to die of competing causes than from lung cancer, especially those that are related to heavy tobacco use, including cardiovascular disease, chronic obstructive pulmonary disease and extrapulmonary malignancy. These same conditions may preclude the patient from effective treatment for an early stage lung cancer. As Young and Hopkins point out, the risk of lung cancer as measured by existing clinical models does not equate to who will get the most benefit of screening (6). They have shown that, although the presence of airflow limitation confers a greater risk of lung cancer, it is also associated with more aggressive lung cancer and higher lung cancer mortality, as well as a greater likelihood of death from a competing cause. One can appreciate the ethical dilemma of clinicians who must balance the patient's lung cancer risk versus their risks of dying of other diseases.

Dr. Tammemägi also addresses the concern by some that lung cancer risk models select a screening population that is more likely to be elderly, in poor health and less likely to benefit from screening compared to the NLST eligibility criteria (7). If the 1/4th of NLST eligible individuals at low risk of lung cancer (6-year incidence proportion =0.008) are excluded, the age, comorbidity count and competing causes of death are similar to those selected by the Prostate Lung Colorectal and Ovarian Cancer Screening Trial (PLCO) m2012 model as having a lung cancer risk of ≥1.5%. The number needed to screen to avert one lung cancer death could be significantly reduced with this approach, and fewer low-risk patients would be screened. Risk modeling can also be used to address health care disparities, e.g., the higher rates of lung cancer in African Americans within the US. Expanded risk prediction models can assess lung cancer risks in patients who do not meet current eligibility criteria, including light smokers, never smokers, and current smokers younger than 55 years.

It is likely that annual screening may not be essential in all screening-eligible individuals. Screening trials have been, understandably, of relatively short duration. The NLST included 3 annual screening CTs; the NELSON trial included 3 rounds of screening over a 5-year period (8,9). The NELSON trial provided the opportunity to assess screening intervals of 1, 2 and 2.5 years. As Drs. Heuvelmans and Oudkerk describe in "*Appropriate screening intervals in low-dose CT lung cancer screening*", prolonging the screening interval in a selected population with a lower lung cancer risk profile could reduce the harms and costs of screening without an unacceptable increase in interval lung cancers (10).

Lung cancer screening in the US became clinically available following the results of the NLST, and reimbursed by third party payers after the US Preventive Services Task Force (USPSTF) recommendation on screening for lung cancer in 2014. In 2015, the Centers for Medicare & Medicaid Services (CMS) issued a coverage memo for lung cancer screening counseling,

shared decision making and annual lung cancer screening but only if a number of criteria were met (11). These included the following:

- Determination of beneficiary eligibility including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting;
- Shared decision making, including the use of one or more decision aids, to include benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;
- Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;
- Counseling on the importance of maintaining cigarette smoking abstinence if former smoker; or the importance of smoking cessation if current smoker and, if appropriate, furnishing of information about tobacco cessation interventions; and
- If appropriate, the furnishing of a written order for lung cancer screening with LDCT.

As Dr. Lowenstein *et al.* point out, the prerequisite of counseling and a shared decision-making visit including the use of decision aids for a preventive health care service is unprecedented in the US (12). The shared decision-making visit is critical in that this is the opportunity to involve the patient in the consideration of his/her personal lung cancer risk, risk of death from other causes, the potential harms of screening and the potential benefits of early detection of lung cancer. Although no one decision aid has been universally adopted, Dr. Lowenstein and her team provide us with a review of currently available decision aids for lung cancer screening, as well as a model of how these can be incorporated into the shared decision-making visit. There are a number of barriers to a successful shared decision-making visit, complicated by the variability in who conducts this visit, and the method and content of the discussion.

The CMS regulations for lung cancer screening stipulate not only that the shared decision-making visit includes counseling on the importance of smoking cessation, but also that the imaging facility make available smoking cessation interventions by current smokers. Current smokers who undergo CT screening for lung cancer express a greater readiness to quit smoking, and report higher quit rates than smokers who are not in screening programs (13). The CT screening process may be considered a "teachable moment" for smoking cessation. Improving quit rates in this population of heavy smokers could have a greater impact on reducing morbidity and mortality than the detection of lung cancer on a screening CT (14). In this issue of *TLCR*, Dr. Minnix *et al.* emphasize the role of extended counseling and/or pharmacotherapy, the routine integration of cessation treatment programs into the screening process, and the multiple opportunities for cessation presented in a supportive environment (15).

The primary goal of CT screening for lung cancer is the detection of a pulmonary nodule that may represent lung cancer. The majority of lung nodules are, however, benign, and the distinction between benign and malignant nodules becomes critical in the acceptance of CT screening and its cost-effectiveness. The high false positive rate experienced in the NLST has been reduced to some extent by raising the threshold for actionable nodules from 4 mm in the NLST and from 5 mm in ELCAP to the 6 mm threshold in Lung-RADS v.1.0 (16-19). In this issue of *TLCR*, Dr. Vlahos *et al.* review the technical parameters that can influence nodule detection, the features associated with benign nodules, and imaging techniques that may be useful in further characterizing indeterminate nodules (20). Drs. Kadir and Gleeson then further explore radiomics/texture analysis and deep machine learning approaches to characterizing indeterminate nodules as either benign or malignant (21). Dr. Clay and his team describe their quantitative analysis tool, Computer Aided Nodule Analysis and Risk Yield (CANARY), that allows non-invasive assessment of tumor characteristics, and potentially risk stratification of pulmonary adenocarcinomas (22).

Biomarkers may play a tremendous role in the future in not only selecting patients for CT screening, but also for diagnosis in patients with symptoms or with indeterminate nodules. In this issue of *TLCR*, Drs. Hanash *et al.* review the variety of biomarkers and biomarker panels currently being developed for use in lung cancer screening (23).

Finally, low dose CT lung cancer screening can result in other clinically significant findings which may impact treatment decisions, morbidity and mortality (24-26). Drs. Ravenel and Nance review detection of coronary artery calcification on CT scans performed for lung cancer screening, and Dr. Godoy *et al.* cover extrathoracic malignancies that can be incidentally found while screening for lung cancer (27,28). It is clear that lung cancer screening with CT provides a unique opportunity to detect other potentially life-threatening disease.

We are pleased to provide this comprehensive review and update of lung cancer screening. It is an exciting time in lung

cancer screening and we hope that these advances in screening will result in further reduction in lung cancer mortality, a decrease in the harms of screening, and improved patient care.

Acknowledgements

None.

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doi: 10.21037/tlcr.2018.06.02
Conflicts of Interest: The authors have no conflicts of interest to declare.
View this article at: http://dx.doi.org/10.21037/tlcr.2018.06.02

Cite this article as: Chiles C, Munden RF. Lung cancer screening: the path forward. Transl Lung Cancer Res 2018;7(3):216-219. doi: 10.21037/tlcr.2018.06.02

