Editorial Commentary

Optimizing selection of candidates for lung cancer screening: role of comorbidity, frailty and life expectancy

Shailesh Advani[1,2], **Dejana Braithwaite**[1]

[1]Cancer Prevention and Control Program, Department of Oncology, Georgetown University School of Medicine, Washington, DC, USA; [2]Social Behavioral Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

Correspondence to: Dejana Braithwaite, PhD. Associate Professor of Epidemiology and Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, 3300 Whitehaven Street, NW, Suite 4100, Washington, DC 20007, USA. Email: dejana.braithwaite@georgetown.edu.

Submitted Apr 23, 2019. Accepted for publication Sep 23, 2019.
doi: 10.21037/tlcr.2019.10.03
View this article at: http://dx.doi.org/10.21037/tlcr.2019.10.03

Lung cancer screening: challenges and opportunities

Lung cancer accounts for nearly 27% of incident cancers in the United States and is the leading cause of cancer-related mortality (1). The overall five-year survival in lung cancer patients is 17% but ranges from 55% for local tumors to 4% for distant tumors (1). In 2011, the US National Lung Screening Trial (NLST) found that, when compared to chest X-ray, three rounds of annual low-dose computed tomography (LDCT) reduced lung cancer mortality by 20% among persons 55 to 74 years old with ≥30 pack-years of smoking history and ≤15 years since quitting (2). Based on these results, both the United States Preventive Task Force (USPSTF) and Centers for Medicaid Services (CMS) recommend lung cancer screening (LCS) for high risk persons. Additionally, USPSTF recommends screening current and former heavy smokers up to the age of 80 years annually, but Medicare limits coverage to adults 55 to 77 years old (3-7). Screening candidates navigating these recommendations are required to engage in a shared decision-making discussion of benefits, harms and uncertainties of screening (8). Because participants enrolled in NLST were younger, better educated, had fewer comorbidities and were more likely to be former smokers compared to the general population, the real-world evidence regarding the effectiveness of LCS remains unclear (9). Similarly, other LCS trials worldwide—including the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), the UK Lung Cancer Screening Trial (UKLS), Lung Cancer Screening Study (LSS), Danish Lung Cancer Screening Trial (DLSCT), German Lung Cancer Screening Intervention Trial (LUSI), Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) and First Brazilian Lung Cancer Screening Trial (BRELT1)—similarly recruited healthier and younger participants compared to the LCS-eligible general population (10-21). Hence, uncertainty exists regarding the benefits and harms across diverse population groups, including stopping age for screening due to differences in demographic and clinical characteristics such as the burden of chronic co-existing illness and functional limitations.

What do clinical guidelines recommend?

Clinical guidelines reflect continued uncertainty regarding the stopping ages for LDCT screening. The American Society of Clinical Oncology (ASCO), the American College of Chest Physicians (ACCP), the American Cancer Society (ACS) and the National Comprehensive Cancer Network (NCCN) guidelines are aligned with the NLST criteria of age 77 as the upper age limit (5,22-24), whereas the United States Preventive Services Task Force (USPSTF) and the American Association of Thoracic Surgery (AATS) guidelines raise the cutoff to 80 years (25,26). Overall, these guidelines offer limited guidance for individualizing LCS decisions as a function of coexisting illnesses. The AATS, ACCP, ACS and NCCN guidelines all incorporate health status into some of their eligibility criteria for LCS; AATS and NCCN recommend screening among individuals with a 20 pack-year smoking history and at least one additional comorbidity that increases the risk

of developing lung cancer, whereas the ACS recommends that eligible individuals should be "in good health" (5,22,25). The ACCP explicitly states that individuals with comorbidities that adversely influence the ability to tolerate screen-detected findings or early-stage cancer treatment should not be screened (24,27). In contrast, the American Academy of Family Physicians does not formally endorse LCS (7). In the aforementioned clinical trials (10-21), participant inclusion age ranged between 50–74 years for patient eligibility in screening trials. Based on modeling analyses, the USPSTF has extended upper age limit for LCS to age 80; USPSTF also state that screening should be discontinued if patients develop a health problem that substantially limits their ability to tolerate lung cancer surgery (28).

Existing evidence on the impact of co-existing chronic illness on LCS outcomes

Evidence from NLST showed that the aggregate false positive rate in NLST was higher among older adults age 65 (65 and over: 27.7% *vs*. under 65: 22.0%); a higher proportion of invasive diagnostic procedures after false-positive screening was also observed by age (65 and over: 3.3% *vs*. under 65: 2.7%) (29). Potential harms of LDCT screening include but are not limited to false positive results, overdiagnosis, and diagnostic and treatment complications due to older age and comorbidity (30-32). Further, simulation modeling by the Cancer Intervention and Surveillance Modeling Network (CISNET) revealed that the rate of overdiagnosis increased with age (33). This finding was consistent across other studies and represents a major concern regarding the implementation of LCS in community practice.

Crucially, nearly a third of the estimated 8.6 million LDCT LCS eligible US screening population present with consequential chronic conditions, including chronic obstructive pulmonary disease (COPD), congestive heart failure and diabetes (34,35). In 2017, the American Thoracic Society convened a workshop to identify research gaps and future directions to optimize selection of candidates for LCS by accounting for co-existing chronic illness (9). Specifically, experts from the fields of oncology, pulmonology, epidemiology and health services research concluded that competing causes of death, including smoking associated comorbid conditions like COPD and cardiovascular disease, are highly prevalent among LCS eligible populations and may limit long term benefits of LCS due to their impact on overall health and life expectancy (9).

A high prevalence of multimorbidity among LCS candidates poses a clinical and policy conundrum. For example, on one hand, persons with COPD face a 2 to 3-fold higher risk of lung cancer than smokers without COPD and may be more likely to benefit from LCS (36-41). On the other hand, persons with advanced COPD are at a greater risk of complications during evaluation of pulmonary nodules (42), have a higher 30-day mortality after resection of lung cancer (especially after thoracotomy) (43,44) and have a higher risk of non-lung cancer mortality (41,45). Given the lack of the real-world evidence, the benefits to those screened with advanced COPD (GOLD grade 3 and 4) remain controversial since findings from an NLST sub-study show rates of respiratory deaths are higher than lung cancer deaths in that population (46). In this study, over 50% participants had risk factors for premature mortality (46)—such results are in in strong contrast to breast cancer screening where comorbid disease is much less prevalent (47,48). Indeed, several comorbid conditions are many-fold more prevalent in populations at high risk of lung cancer (i.e., NLST) including chronic lung disease (4–5 folds), diabetes (2–3 folds) and heart disease (2–4 folds), relative to populations at risk of breast cancer (47,49). This means that the benefits from CT screening are not linearly related to the risk of developing lung cancer and that smokers at highest risk derive less benefit from screening than those in the intermediate level of risk (49).

Moreover, Howard *et al*. also reported that the US population eligible for LCS may benefit less from early detection than NLST participants due to a higher risk of death from competing causes (35). This emphasizes the need to tailor LCS among eligible populations based on a person's comorbidities and functional status. While much research has focused on estimates of lung cancer risk there is a paucity of research on how to optimize LCS decisions among patients with comorbidity (36).

Crucially, simulation modeling analyses have identified the significant impact of comorbidity and life expectancy on the net benefits of cancer screening in the elderly (50,51). While the majority of extant lung cancer risk prediction models rely primarily on age and smoking history, the $PLCOM_{2012}$ model also includes several comorbid conditions, including COPD (52). In another modeling analysis among patients with COPD in a LCS setting, authors determined that lowering inclusion criteria for smoking pack-years for these high risk patients may provide

additional benefits in terms of mortality reduction (44). Consequently, there is a growing interest in measuring relevant comorbidities among LCS populations to better quantify benefits and harms associated with screening, including evaluation of potential diagnostic and treatment-related complications (53,54).

Importance of measuring frailty among LCS candidates

Frailty is defined as "an extreme vulnerability to endogenous and exogenous stressors that exposes an individual to a higher risk of negative health related outcomes" (55). Since lung cancer is a disease of aging and the frailty burden increases with age, evaluating frailty in the LCS setting may help identify subgroups of patients less likely to benefit from screening (56). Domains that underlie the frailty syndrome have been utilized in geriatric research over the years and includes combination of strength, balance, motor processing, cognition, nutrition, endurance and physical activity (57). Hence a comprehensive assessment of both physical and cognitive domains helps cover global dimensions of frailty and its impact on health outcomes. Prior studies have pointed to significant associations of frailty with poor cancer screening outcomes (58), response to surgery (59), chemotherapy and overall mortality and morbidity (60,61). Moreover, as frailty impacts life-expectancy, understanding benefits and harms associated with LCS by levels of frailty remains an important gap in LCS research.

Future directions and conclusions

A significant challenge in risk-based screening is how to incorporate comorbid conditions into estimates of benefits and harms of LCS. This is especially true of elderly patients who are more likely to have comorbid conditions that might lead to harms related to diagnostic procedures and treatment of screen-detected cancer (62). For example, while patients with COPD are at increased risk of death from lung cancer and therefore have the most to gain from LCS, having chronic lung disease also reduces the net benefit of screening by limiting life expectancy and by increasing the risk of complications from downstream diagnostic procedures and surgical treatment. Incorporating information on potential LCS benefits and harms with patient preferences in a shared decision-making setting—as proposed by Caverly *et al.*—might optimize selection of LCS candidates (63).

Another promising strategy to facilitate risk-based screening relates to integration of biomarkers as potential diagnostic tools for lung cancer; these include microRNAs, tumor associated antibodies or TAAs, epigenetic markers including DNA methylation, cell-free circulating DNA and immune response biomarkers including C4d complement split product (termed as C4d protein) (64-66). If biomarkers were available to improve sensitivity and specificity of LCS, they could inform strategies to reduce the risk of harms due to downstream procedures among LCS candidates with comorbid conditions.

Conclusions

In sum, recent advances in LCS using LDCT demonstrate that it is increasingly possible to detect lung cancer, a common and deadly disease, at an early stage—thereby reducing morbidity and mortality. Still, the real-world implementation and dissemination of LCS is hampered by the fact that we do not have basic information on the impact of LCS in the real-world, i.e. in the population with a high comorbidity burden that is subject to LDCT screening. Further research is needed to quantify the benefits and harms of LCS in the subpopulation with co-existing chronic illness.

Acknowledgments

The authors would like to acknowledge Anthony Chicaiza for his assistance on this manuscript.
Funding: Dean's Toulmin Pilot Projects and Partners in Research Awards, 2018, Georgetown University Medical Center.

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.

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Cite this article as: Advani S, Braithwaite D. Optimizing selection of candidates for lung cancer screening: role of comorbidity, frailty and life expectancy. Transl Lung Cancer Res 2019;8(Suppl 4):S454-S459. doi: 10.21037/tlcr.2019.10.03

