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Emphysema Detection in the Course of Lung Cancer Screening: Optimizing a Rare Opportunity to Impact Population Health

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Recent research has clarified that emphysema is a component of the spectrum of chronic obstructive pulmonary disease (COPD) and that new approaches, especially with early disease, are required to address the profound health burden of this complex heterogeneous disease (1–4). This is relevant to lung cancer screening (LCS) as recent publications report

that the computed tomography (CT) scans obtained for LCS also frequently detect emphysema. COPD and lung cancer are among the top five causes of premature death in the United States and across the world (5, 6). Furthermore, tobacco-exposed individuals are at risk for lung cancer and COPD (7, 8). In routine clinical care, most cases of COPD are diagnosed as a result of symptom-prompting and are found with advanced disease.

Two recent reports analyze data from two separate large screening cohorts, including IELCAP (International Early Lung Cancer Program) and NLST (National Lung Screening Trial), respectively. These two cohorts include a total of more than 79,000 participants undergoing LCS (9, 10). The radiology reports of baseline LCS scans from

those two cohorts revealed a frequency of emphysema detection of 23.8% and 31%, respectively. In the IELCAP analysis, 87.3% of all screening participants had no prior history of COPD/emphysema, which meant that of the 12,542 screening participants found to have emphysema, 9,595 (76.5%) of those cases had no prior diagnosis of COPD (9). Of the NLST participants, of the 25,002 screening participants who underwent thoracic CT evaluation, 89.4% had no prior history of COPD/emphysema (10). Of the 30.7% of the NLST screening participants found to have emphysema on baseline CT scans, 82% of the cases were found in participants with no prior history of COPD/emphysema (10). Therefore, LCS participation resulted in frequent detection of emphysema in these two screening cohorts, and typically, screening

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participants had no prior awareness of this pulmonary disease (9, 10).

Implications of Routine Emphysema Detection with Thoracic CT Screening

Long-term studies have reported that the finding of emphysema, even in spirometrically normal persons, is associated with increased symptoms and worse quality of life (11–14). Individuals with visible emphysema detected by CT are also at increased risk of death and progressive airflow obstruction compared with those without (12–14). Many studies report important clinical correlations associated with the spectrum of COPD and emphysema, including increased risk for lung cancer, progressive pulmonary debility, and death (7, 15–20). When a standardized visual grading system is used, the risk of death clearly increases with emphysema grade (21).

Recently, the USPSTF (United States Preventive Services Task Force) has revised its recommended eligibility requirements for LCS to individuals who are aged 50–80 years (55–80 previously) and have at least 20 pack-years (30 previously) of smoking history (22). On the basis of this new CMS (Centers for Medicare and Medicaid Services) recommendation, 15 million individuals are now eligible for LCS. A consequence of the new CMS extended screening eligibility will be the detection of a vast new population of individuals who will be found to have generally asymptomatic emphysema (23). If CT-based LCS were fully implemented, using a conservative estimate of emphysema frequency of 20–30%, in which 75% were in asymptomatic screening participants as already discussed, perhaps as many as 2.6–3.0 million would learn that they have emphysema detected (9, 10). Although national LCS uptake is proceeding slowly, there is currently a window for this new information about the frequent detection of emphysema to be integrated with the other relevant information shared with individuals considering participation in LCS.

How Could This Newly Diagnosed Group of Patients with Emphysema Be Managed?

Currently, there are no widely-disseminated LCS protocols for the detection or

management of emphysema, as well as no standards for communicating emphysema results to screening participants. This situation complicates understanding the full extent of screen-detected emphysema. To address these issues, steps to standardize radiological reporting of emphysema, as well as measures to improve communication about the frequency of emphysema detection within the LCS process, are critical priorities.

This new screening situation with frequent early detection of emphysema in the course of LCS may evolve more cohesively if delivered within a population health paradigm. From an LCS participant's perspective, there are potential structural disease-specific management barriers implicit in the current single-disease cancer screening approach. This is a critical emerging issue as an estimated 29 million Americans aged 20–79 are living with obstructive lung disease. However, only 13 million of these adults are aware of their diagnosis (24). The overlap of LCS, COPD, and emphysema is an exemplary opportunity to demonstrate the benefits of a holistic population health approach. The hazards of not considering disease overlap go beyond diagnosis, as the leading causes of mortality for individuals with COPD are, first, cardiovascular disease and then lung cancer (5, 6, 16, 17). Recently it has been reported that LCS enhanced the success of smoking cessation, and this prevention intervention could benefit both lung cancer, emphysema, and cardiovascular disease (25). Medicine is rarely gifted with such a high-yield opportunity to move beyond the individual disease silo to better manage these shared comorbid conditions. Therefore, LCS provides a new setting for comprehensive research, especially with underused preventive measures such as tobacco cessation, to better define the management of these shared comorbid conditions (4).

Current State of COPD Screening

The recently updated USPSTF recommendation for COPD screening continues to discourage COPD screening in normal-risk, asymptomatic adults (26, 27). This recommendation covers the use of questionnaires and peak flow or pulmonary function testing for detecting COPD but does not evaluate the use of thoracic CT (26, 27).

The current U.S. national implementation of LCS uses thoracic CT to evaluate for lung cancer, but the acquired CT scan will be routinely evaluated for emphysema (28). Generally, the acquired LCS CT imaging data is analyzed for emphysema because of medical legal concerns with missing important diagnoses. Regardless of the motivation, the results of this emphysema evaluation still must be shared with the screened individual. This situation, therefore, constitutes a *de facto* form of emphysema screening for this high-risk, tobacco-exposed, screening-eligible cohort (22, 23). Emphysema screening as a byproduct of LCS is a unique situation from a cost–benefit perspective, as the imaging cost, medical radiation exposure, and the time burden of acquiring a CT scan to detect emphysema already accrued.

A complex issue with this situation is how to best communicate to the public about the implications of frequent emphysema detection, as we are already engaged in the national implementation of LCS. Typically, with LCS at baseline, lung cancer is only detected in about 1% of participants, so the detection of pulmonary emphysema will be markedly more frequent than the diagnosis of lung cancer in the process of LCS. Currently, this emerging reality with frequent emphysema detection within LCS is not mentioned in guidelines or shared decision tools about LCS or management.

The recent USPSTF recommendations for LCS were influenced by the results of the NELSON LCS trial but did not include a discussion on the impact of emphysema detection in the setting of LCS cancer screening, although it was also observed by the NELSON group (29, 30). The successor trial to the NELSON randomized LCS trial has been ongoing in Europe and Asia for several years and is using thoracic CT to simultaneously evaluate for emphysema and using emphysema and air trapping as biomarkers for COPD while detecting early lung cancer (29, 30).

What Can We Do about LCS-detected Emphysema Now?

In the LCS setting, participants typically would be fully functional and routinely able to engage in nonpharmacological interventions such as smoking cessation. The existing recommendation for individuals in the eligible-for-screening age group already included increasing physical activity, and emphysema detection could reinforce the

Table 1. Potential screening participant benefits of early detection of emphysema and related pulmonary injury from a lung cancer screening encounter

- Provides additional personalized motivation for tobacco cessation in current smokers to mitigate lung cancer risk, limit emphysema progression, and preserve lung tissue from further destruction, as well as limit progression of other tobacco-related chronic diseases such as coronary artery disease.
- Provides earlier recognition for primary care providers to identify individuals who would benefit from detailed symptom screening to prompt spirometric assessment for COPD detection as well as to encourage screening compliance to detect early lung cancer.
- May also provide additional motivation by reinforcing other existing preventive recommendations, such as increasing physical activity or complying with vaccination to reduce the burden of respiratory infections.
- Empowers screening subjects to use their personalized health information obtained from the analysis of CT scans to improve their own health, which in turn may improve annual LCS adherence.
- May allow for personalizing additional nonpharmacological interventions for subsequent rounds of LCS to evolve the annual LCS encounter to allow more screening participant engagement in annual health checks.

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; LCS = lung cancer screening.

motivation for this recommendation. This would seem relevant as it is a preventive measure known to improve cardiovascular outcomes, and cardiovascular disease is the leading cause of death for patients with COPD (17, 18).

In addition, there is an important need to address the lack of systematic diagnostic reporting for emphysema detection. The IELCAP has proposed a standardized approach to emphysema evaluation by LCS CT, which may provide a useful starting point for more consistent detection of emphysema (9, 31). The Fleischner Society also recently proposed a simple means of classifying emphysema severity visually, which has been reported to achieve good interrater reliability (21, 32). Thoughtful efforts are required to establish consensus in defining optimal reporting of screen-detected emphysema (12–21).

Fortunately, there has been much progress in optimizing objective clinical emphysema/COPD detection using quantitative thoracic CT scanning (33, 34). Advanced computer analysis and standardization of CT acquisition protocols have identified quality standards as well as

thresholds for defining the regional extent of emphysema (35–42). Recently, the contribution of image quality to robust analyses was illustrated in a large, well-designed meta-analysis that found both visual and quantitative detection of emphysema on thoracic CT images were significantly correlated with lung cancer risk (43). For near-term generalizability of emphysema detection, visual assessment of emphysema by radiologists is straightforward and can readily be implemented in clinical practice. In the near future, quantitative emphysema assessment has the potential for more reliably monitoring change in emphysema progression status over time and will be critical to support research in defining effective approaches to early disease management (9, 10, 22, 37, 41, 42).

Interventions for COPD Management

From a pharmacologic therapeutic perspective, the USPSTF concludes that evidence for the benefits of pharmacologic interventions is marginal (26). The USPSTF

did not find conclusive evidence that nonpharmacologic interventions resulted in mortality reduction, but they did not find evidence of significant harm. Although the USPSTF acknowledged that physical activity did have proven benefits, such as with cardiovascular conditions, they also noted a paucity of quality prevention research studies for COPD/emphysema (26, 27, 44).

Moving Forward

Table 1 summarizes the potential benefit that may emerge from the detection of emphysema during LCS. For example, the personalized CT results may be shared with an LCS participant, especially when new objective findings of unsuspected emphysema are detected in an individual who continues to smoke. Awareness of this additional evidence of tobacco harm resulting in emphysema may reinforce the profound importance of smoking cessation in the LCS setting (26, 27, 45). Annual LCS may also provide a valuable research setting to explore objective benefits with other preventive interventions, such as physical

Table 2. Recommended next steps for the detection of emphysema in the course of lung cancer screening

1. Communicate to the public and medical community that there is already frequent detection of emphysema in the course of lung cancer screening.
2. Engage relevant bodies such as USPSTF and professional societies to recognize the research and preventive intervention opportunities with combined detection of lung cancer and emphysema with thoracic CT screening in the high-risk population.
3. Establish standardized reporting with pulmonary and thoracic professional societies to assist referring clinicians moving forward to appropriately tailor the management of different extents of emphysema found on screening thoracic CT scans.
4. Support additional research on improving thoracic CT detection and management, including workflows, on emphysema and other tobacco-related conditions identifiable with thoracic CT scans.
5. Support further research on using annual screening results to investigate both pharmacological interventions as well as nonpharmacologic interventions in diverse populations, such as with programs for iterative tobacco cessation approaches and increased physical activity.
6. Promote the measurement of screening outcomes for relevant tobacco-related conditions and include appropriately selected outcomes in payers' population-based reimbursement and quality models to incentivize the continued evolution of effective, economical, and equitable detection within thoracic CT screening.

Definition of abbreviations: CT = computed tomography; USPSTF = United States Preventive Services Task Force.

activity. Cardiovascular disease and lung cancer are the leading cause of death for patients with COPD (17, 18). Strong evidence does exist for physical activity improving mortality outcomes for cardiovascular disease, together with moderate benefit for physical activity reported for lung cancer (46). For LCS-eligible cohorts, it is essential to recall that preventive interventions, such as physical activity, are already recommended because this intervention is economical, generally safe, and accessible. Such information may be of interest to many LCS participants, especially for individuals detected with previously unsuspected emphysema (46). We speculate that the additional imaging data extracted from the annual thoracic CT scans may encourage screening participants to engage more consistently with measures to improve their health, including greater compliance with the annual LCS encounter.

We acknowledge that the evidence basis for formulating the best management for LCS-detected emphysema is imperfect. We contend that this situation is similar to Alzheimer's disease care, in which physical activity interventions, although

not fully validated, are promising and broadly encouraged in the Alzheimer's setting. The situation with Alzheimer's is also challenged by the absence of highly effective pharmacotherapy (47).

However, for emphysema, as with Alzheimer's, there is a critical need for further research to optimize intervention approaches. Leveraging preventive interventions for the diverse LCS participants who experience many tobacco-related comorbidities seems prudent as research proceeds on how to best optimize the benefit of already approved LCS. To achieve this goal, communication efforts to educate the public about the implications of thoracic imaging-based screening in the heavily tobacco-exposed cohort are timely, especially if linked to a continuous process improvement with clinicians and professional societies to define broader tobacco-related thoracic management as outlined in Table 2. Clearly, this situation highlights the urgent need for research investment across the spectrum of COPD/emphysema, as was outlined in the recent Lancet-commissioned white paper (4).

Conclusions

Recent publications demonstrate that emphysema can be frequently detected by thoracic CT scans performed for LCS. The joint detection of these two frequent lethal tobacco-related diseases provides a new opportunity to manage these diseases in a more cohesive fashion that may enhance the public investment related to the delivery of national LCS. For individuals considering participation in annual LCS, information about the frequent detection of other significant imaging findings, such as emphysema, must be routinely discussed as it is a major health determinant. Detecting emphysema, like detecting early-stage lung cancer, may allow important opportunities for tobacco-exposed individuals to manage their lung health using safe and economical preventive interventions. ■

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