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Comments on National Coverage Analysis (NCA) for Lung Cancer Screening with Low Dose Computed Tomography (CAG-00439N)
Provided by members of the National Lung Screening Trial Research Team

In response to the public comment period opened by the Centers for Medicare and Medicaid Services regarding lung cancer screening, members of the National Lung Screening Trial (NLST) Research Team are providing data from additional analyses of the NLST. These data are in review for publication in a US medical journal; in the interests of the NCA, we are providing this information prior to publication.

The US Preventive Services Task Force (USPSTF) Grade B recommendations for screening advocate annual screening for lung cancer in current or former cigarette smokers between the ages of 55-80 years with a minimum 30 pack year smoking history, and among former smokers, those having quit within the preceding 15 years (1). At present, there are preliminary data using risk prediction models for lung cancer death designed to enrich the screening population for those at greatest risk (2); these models are new and address factors of screen eligibility. Our comments relate to the presence and characteristics of lung nodules seen on screening, which will be subject to revision based on collective experience.

Our intention with this comment is to inform potential approaches to screening recommendations in the screen-eligible population as defined by the USPSTF recommendations. The data we now present are based on more detailed analyses of the relationships between nodules and the ultimate diagnosis of lung cancer. Our analysis was designed to: 1) determine the relative proportions of CT-screened participants with and without nodules that developed lung cancer and 2) determine the associations between a nodule observed at baseline screen and the time to diagnosis of lung cancer. We stratified our results according to the consistency of nodules, characterized as solid nodules, part-solid nodules (PSN) and ground glass nodules (GGN); nodule size (longest axial diameter); and other features that included anatomic location, margin characteristics, and the level of suspicion for lung cancer based on the interpreting radiologists’ subjective level of suspicion (on a 5-point scale). We analyzed time to lung cancer diagnosis in order to quantify the time-varying effects of different nodule consistencies. Note that only nodules in the range of 4-30 mm longest axial diameter were considered “positive” screens, and we limit our information to nodules within this size range.

Overview

Trial-wide, 11,128 nodules of 4 mm diameter or larger were recorded at baseline (T0) screen, 11,190 nodules at the 1-year screen (T1), and 11,457 nodules at the 2-year screen (T2). At T0, 8811 solid nodules, 1807 ground glass nodules, and 510 part-solid nodules were reported in 6726 individual participants.

Lung cancer was diagnosed at some point in 61 (6.0%) of 1012 individuals with only GGNs, 34 (13.6%) of 250 participants with only part-solid nodules, 551 (8.1%) of 6800 participants with only solid nodules, and 186 (9.6%) of 1932 participants with more than one nodule consistency. Finally, 244 (1.5%) of 16,461 participants in whom no nodule 4 mm diameter or larger was detected during the three annual screens were ultimately diagnosed with lung cancer at some point during the years of follow-up (median 6.4 years).

Participant-Level Findings

Lung cancers were ultimately diagnosed in 196 participants with GGNs, including participants with only GGNs and participants with multiple nodule consistencies. Lung cancers were roughly equally
observed in the same lobe as the GGN as in different lobes (52.6% and 47.4%, respectively). Part-solid nodules observed at any time point were associated with a lung cancer diagnosis in 135 participants, more commonly in the same lobe as the PSN (76.3%). Solid nodules observed at any time point were associated with a lung cancer diagnosis in 719 participants, also more commonly in the same lobe as the solid nodule (72.9%).

Rates of lung cancer diagnosis varied by nodule consistency at the T0 screen (Fig. 1). Among participants with no nodules 4 mm diameter or larger at T0 the rate of cancer was low, reaching 2.9% at year seven. Among participants with only one consistency of nodule, those with PSNs had the highest rate, showing an initial steep rate that peaked at 14 months from first observation. Participants with solid nodules also demonstrated an initial steep rate of lung cancer diagnosis peaking at approximately 4 months from detection. With GGNs, the rate of lung cancer was slower, but persisted over time. After year six, individuals with baseline GGNs had higher rates of cancer than those with solid nodules. Finally, individuals with nodules of multiple consistencies had the highest rate of lung cancer diagnosis after the first 22 months. By year seven, 16% of these participants were diagnosed with lung cancer; rates of diagnosis varied by the combination of nodule consistency, but was highest among those with part-solid nodules.

Nodule-Level Findings
At the nodule level and across all consistencies at T0, nodules in the same lobe as the lung cancer were most commonly in the right upper lobe (solid nodules 66.2%, part-solid nodules 62.5%, GGNs 39.0%). Lung cancer in the context of GGNs were more evenly distributed throughout the lungs than the other consistencies. An upper lobe predominance of lung cancer was observed at all three screening time points.

Baseline nodules ultimately associated with lung cancer tended to be larger than nodules not associated with cancer for all nodule consistencies (p < 0.0001)(Table 1). The range of nodule diameter when first observed was large in all three groups. Rates of lung cancer diagnosis at year one were low across all nodule consistencies for nodules 4-6 mm diameter (Fig. 2).

A generalized linear mixed regression model was used to predict lung cancer in the same lobe as a screen-detected nodule at T0 (Table 2). For GGNs the odds ratio of lung cancer in that location was 0.654 relative to a solid nodule (p < .0077). For nodules detected in an upper lobe, the odds of lung cancer in that location were 3.815 relative to a middle lobe nodule (p < 0.0001) and 1.671 relative to a lower lobe nodule (p < 0.0001). Spiculation or poorly defined margins increased the odds by 2.796 relative to a smooth margin (p < 0.0001); the odds increased by 1.48 for every 1-mm increment in diameter above 4 mm. Finally, among participants in whom the suspicion for lung cancer was provided by the interpreting radiologist, a high or moderately high level of suspicion for lung cancer increased the odds by 9.739 relative to low or no suspicion (p < 0.0001).

| Table 2. Generalized Linear Mixed Logistic Regression to Model Lung Cancer Diagnosis in the Same Lobe as a Detected Nodule at T0 (11,128 nodules from CT participants with T0 screen) |
|---|---|---|---|
| **Nodule Features** | **Odds Ratio** | **95% confidence Limits** | **P-value** |
| Consistency: Ground glass vs. solid | 0.654 | 0.479 | 0.894 | 0.0077 |
| Consistency: Part-solid vs. solid | 1.011 | 0.663 | 1.541 | 0.9605 |
| Location: Upper vs. middle lobe | 3.815 | 2.451 | 5.937 | < .0001 |
| Location: Upper vs. lower lobe | 1.671 | 1.306 | 2.137 | < .0001 |
| Nodule count per scan (per each additional nodule) | 0.897 | 0.823 | 0.978 | < .0001 |
| Margins: Spiculated or poorly defined vs. smooth | 2.796 | 2.132 | 3.667 | < .0001 |
| Nodule longest axial diameter | 1.148 | 1.125 | 1.171 | < .0001 |
| Radiologist level of suspicion for lung cancer | 9.739 | 5.491 | 17.271 | < .0001 |
| Intermediate vs. low/no | 2.348 | 1.357 | 4.063 | 0.0023 |

This model includes only participants with nodules at T0 and is performed at the nodule level.

1 Level of suspicion of lung cancer was recorded on screening interpretations in the subset of participants enrolled by ACRIN-NLST, N = 3533. Level of suspicion was recorded using a 5-point Likert scale and was assigned at the participant level on interpretation forms. For purposes of analysis, if multiple nodules were detected on the T0 screen, all were assigned the same rating of suspicion.
Figure 2. Rates of Lung Cancer in the Same Lobe as a T0 Nodule Based on Nodule Consistency and Size. Across all nodule consistencies, rates of cancer diagnosis in the same lobe as a nodule observed at the T0 screen were low in the first year. The timing of diagnosis does not necessarily reflect the earliest time point that a cancer could be determined, but rather, the point at which diagnosis was conclusive.

Caveats

The NLST provided conclusive evidence of a 20% relative reduction in lung cancer mortality with CT screening (3). This benefit, the most significant paradigm change in reducing the burden of lung cancer independent of smoking cessation, comes at the cost of a high false positive rate when using a nodule diameter of 4 mm or larger to define a positive screen. Our analysis provides insights into the relationships between nodule features and the diagnosis of lung cancer.

The presence of a 4-30 mm nodule of any consistency was associated with a RR of lung cancer of 5.6 compared to screens with no nodules. Solid nodules accounted for 68% of all nodules, were more commonly associated with lung cancer, but were least specific. Part-solid nodules had the highest positive predictive value (13.7%) for lung cancer, confirming the results of prior studies.

In the NLST, the rate of lung cancer with solid and part-solid nodules was higher soon after baseline screening, but decreased over time. In patients with GGNs, the lung cancer rate was relatively constant, and after six years exceeded that of participants with solid nodules. Additionally, in screeners with a GGN, lung cancers occurred as often in different lobes as in the same lobe as the observed GGN. These observations suggest that GGNs are an imaging biomarker of field of injury and an increased risk of lung cancer; all regions of lung, not just the GGN, are vulnerable to the stepwise progression to lung cancer.
Several observations from this analysis have implications for establishing rational screening intervals and duration. First, more than half of lung cancers were associated with nodules 10 mm or larger across all nodule consistencies. Rates of cancer diagnosis in nodules < 6 mm were very low in the first year following the T0 screen. Establishing higher size thresholds (e.g., 6 mm maximum diameter) for screen positivity may not significantly reduce sensitivity or delay diagnosis. Second, participants with negative screens at baseline exhibited a low rate of lung cancer diagnosis, suggesting that increasing the time interval (up to two years) between screens in this subset may be appropriate. Third, participants with GGNs have a long-term risk of lung cancer and may require some form of long-term surveillance. Finally, the level of suspicion for malignancy by the interpreting radiologist was among the strongest predictors of developing lung cancer, reflecting the importance of radiologist expertise in the performance and interpretation of CT screening examinations.

Limitations

A limitation of our analysis is that mapping between individual nodules reported on the screening CT scans and the diagnosis of lung cancer is incomplete. Screening interpretations reported nodules by anatomic locations and whether they were present on prior screens, but it is not known whether a nodule seen at one time point and in a specific location was the same nodule described in that location at a subsequent screen, or was the nodule later diagnosed as lung cancer. For this reason, evolutionary features likely to be critical to determining the malignant potential of a nodule, such as growth or change in nodule consistency, are not provided. More explicit mapping will require reanalysis of the source images and correlation with diagnostic tests and resection specimens.

Secondly, the rates of cancer diagnosis relative to the observation of a nodule at the T0 screen do not necessarily reflect the earliest time point at which cancer could have been diagnosed, but rather the time interval from first observation to the time of definitive diagnosis in the NLST. Given that half of cancer diagnoses were established in nodules > 10 mm, many of the subcentimeter nodules exhibited growth or other suspicious change over time.

To optimize the effectiveness of CT screening for lung cancer, several practices will be important moving forward. Foremost, screening should be undertaken only if data is routinely collected regarding screening results, nodule features, ultimate diagnoses, and outcomes, such as through observational registries. Screening centers must have expertise in radiologic interpretation as well as access to coordinated multidisciplinary teams experienced in the diagnosis and treatment of patients with lung cancer. The decision to screen and the implications of screening results should be based on a discussion between patients and providers that includes the benefits and risks to screening, including radiation exposure, the potential for false positives, some degree of overdiagnosis, and opportunity costs. Finally, smoking cessation counseling should be implicit to every screening program.

References


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