The International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC) Response to the USPSTF Recommendations

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Lung cancer remains the most lethal cancer across the world. Almost 90% of those cancers are thought to be the consequence of prolonged exposure to tobacco-combustion products. The USPSTF recent draft recommendations of the statement on lung cancer screening, recommended the use of low-dose CT (LDCT) screening in certain populations of current and former smokers, which were otherwise healthy, as a cancer-screening approach. This recommendation was buttressed by a large body of information, but most significant was the large, randomized National Lung Screening Trial (NLST),4 which reported a reduction in tobacco-related lung cancer mortality of 20% after 6 years of follow-up after a baseline and two annual follow-up rounds of CT screening.

IMPLICATIONS OF THE IMPLEMENTATION OF CT SCREENING IN THE UNITED STATES

The USPSTF draft recommendation is a welcome endorsement of LDCT screening to combat a devastating disease. The recommendation considered the effectiveness of CT screening in reducing mortality, the performance characteristics of CT screening, the effectiveness of surgical resection in early-stage disease, and the harms of both screening and surgical resection. However, these recommendations go beyond a restatement of reduced lung cancer mortality in high-risk individuals; they challenge the U.S. health care system to continue to improve the CT screening process as implementation begins. Several unanswered questions that will determine the ultimate success of implementation are proffered. These include the appropriate risk groups to consider, the effects of screening in different demographic subgroups, cost effectiveness, the modeling of radiation effects, methods to improve the discrimination between benign and malignant nodules, the incorporation of biological markers, the integration of intensive tobacco cessation for persistent users, and the psychological consequences of screening on health behaviors and in clinical practice. The Task Force encourages screening in high-risk individuals while concurrently appealing to the medical work force to better delineate the benefits to risks of lung cancer screening. This will require that U.S. screening centers commit to
collecting the necessary demographic, clinical, imaging, tobacco cessation, and outcomes data to inform these unanswered questions in the process of screening implementation.

IASLC Statement

The IASLC has previously supported research into CT screening trials in the light of the public health burden of lung cancer. Each national health service now has an opportunity to decide its own way forward regarding the merits of CT screening based on their interpretation of the existing NLST data and information from other lung cancer screening trials. However, the IASLC makes the following statements: First, the implementation of any screening process should be performed incorporating best practice for screening care in centers that are able to achieve excellence in providing this service and that have a multidisciplinary group of experts focused on this problem. In discussions about screening, for those who have not done so, smoking cessation is the most important measure available to improving overall health outcomes. For former smokers considering lung cancer screening, it is clear that the increased risk of developing lung cancer is diminishing but lifelong.5

The IASLC SSAC recommends that the following current issues should be considered by national health service providers as they consider implementing lung cancer screening:

Cost Effectiveness

The cost of providing lung cancer screening is related to the process of screening delivery. Preliminary modeling studies in the United States have shown that providing lung cancer screening according to best available practice could be delivered cost effectively.6 Valid cost-effectiveness data will ultimately drive the success of implementation in many countries, balancing the incremental cost that lung cancer screening will exact on health care systems with improved health outcomes. We await cost-effectiveness data from the NLST and Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial data. Moreover, the cost-effectiveness of lung cancer screening can be further improved by the addition of smoking cessation counseling.7

Radiological Protocol for CT Screened Nodules

Size quantification on serial CT scans for lung cancer screening is helpful in evaluating whether a pulmonary nodule is benign or malignant. Evaluation of suspicious lung nodules involving the use of quantitative CT imaging, which allows discrimination of rapidly growing nodules that may be cancer from slower growing nodules that are not likely to evolve into cancer, is a developing field and the way forward. Many investigators have suggested that quantifying whole nodule volume could solve some of the limitations of diameter measures8,9 and many studies have explored the value of volumetry.10–13 The rigorous applications of volume measurement guidelines will most likely lead to more accurate management of the lung cancer screening process.

Selection Criteria for CT Lung Cancer Screening Programs in the United States

The NLST eligibility criteria were based largely on age (55–74 years) and heavy-smoking history (≥30 pack-years) among current and former smokers (<15 years since quitting). However, as indicated in the USPSTF document, future research should include identifying methods for focusing LDCT screening on persons at higher risk for disease, to improve test sensitivity, specificity, and cost-effectiveness. Several risk-prediction models have recently been described to better define the optimal risk cohort,14–17 including the model developed using the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial data.15 This model improved the sensitivity of LDCT relative to the NLST selection criteria (83.0% versus 71.1%, p<0.001) and its positive predictive value (4.0% versus 3.4%, p=0.01) without loss of specificity or decrease in mortality reduction. Furthermore, a more recent analysis of the NLST data reported that the prevention of lung cancer deaths in the LDCT screening arm as compared with that in the radiography arm increased according to risk quintiles, with 60% of participants at the highest-risk quintiles 3 to 5 accounting for 88% of the screen-prevented lung cancer deaths, whereas 20% of participants at lowest-risk quintile 1, accounting for only 1% of lung cancer deaths.18 These results suggest that the application of risk-prediction models could reduce the number of individuals that need to be screened to prevent one lung cancer death, reduce false-positive rates of screening, and improve the overall cost-effectiveness of lung cancer screening.

Fitness Criteria and Upper Age Limit

The imposition of any arbitrary upper age limit in selecting patients for inclusion in a LDCT screening program is certain to be challenged by patients and their advocacy groups. The use of age is a discredited and inaccurate surrogate for an assessment of “fitness” or comorbidity. In addition, any upper age limit, such as that of 79 years proposed by the USPSTF, will be revised as we better define the demography of the most appropriate screening cohorts (http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcandraftrec.htm).

However, it is reasonable to assess fitness before entry to a screening program and at key intervals thereafter to ensure that (1) screenees are able to undergo, with tolerable risks, both the investigations indicated to evaluate suspicious nodules and the subsequent treatment of suspicious nodules or proven lung cancers, and (2) their life expectancy because of comorbid disease(s) will not prematurely limit their life expectancy relative to the treatment of a documented lung cancer.

Lung Cancer CT Screening—Considerations of Benefits and Harms

The NLST has shown clearly that LDCT benefits patients by reducing lung cancer mortality and that this also reduces all-cause mortality. Harms may result from physical and psychological sources in the context of discovery of nodules, their workup, and overdiagnosis. The latter is especially important, as all these harms that apply to life-limiting cancer apply to overdiaagnosed cancer with none of the benefits, except smoking cessation. It is important to take into account the influence of comorbid conditions as NLST showed that individuals with multiple comorbid conditions did not benefit from CT screening.18 This effect can be reduced through careful fitness assessment as outlined above. Harms can also be reduced by the
method of workup of nodules. NELSON has shown that the frequency of invasive procedures can be minimized by a protocol to assess growth using CT volumetry at 3- and 12-month intervals depending on the size of the nodule detected.\(^{19}\)

With modern radiological techniques, radiation dose is low, and likely to be even lower in the future. However, it is important to ensure adherence to low-dose protocols by ensuring that those managing screening programs are well versed in contemporary CT dose-reduction techniques as well as the selective use of further diagnostic imaging.

**CCOP Guidelines on Lung Cancer Screening**

The CCOP have also undertaken an in-depth system of review of the screening trials and formulated their guidelines.\(^{2}\) In essence, many similarities with the USPSTF, except they have remained with the NLST selection criteria based on smoking history and age 55 to 74 years. The working group endorsed the NLST criteria, however, it did emphasize that patient acceptability, cost effectiveness, feasibility, and systems capacity would in time indicate whether these parameters were reasonable. The group also recommended that high-risk individuals should be screened for 2 consecutive years and then once every 2 years after a negative scan, based on evidence from the Multicentric Italian Lung Detection Trial (MILD) trial, which did not demonstrate a shift to higher-stage disease with biennial screening compared with annual screening.\(^{20}\) They make a particular point that opportunistic screening should not take place and that screening should only be undertaken in centers of excellence.

**Planned Recommendations from IASLC SSAC**

The IASLC SSAC hosted the second CT Screening before the World Conference on lung cancer in Sydney 26–27 October 2013, where all of these issues were considered fully and recommendations will be provided for the international membership.

**REFERENCES**