

International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 Report

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Abstract: The International Association for the Study of Lung Cancer (IASLC) Board of Directors convened a computed tomography (CT) Screening Task Force to develop an IASLC position statement, after the National Cancer Institute press statement from

the National Lung Screening Trial showed that lung cancer deaths fell by 20%. The Task Force's Position Statement outlined a number of the major opportunities to further improve the CT screening in lung cancer approach, based on experience with cancer screening from other organ sites.

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The IASLC CT Screening Workshop 2011 further developed these discussions, which are summarized in this report. The recommendation from the workshop, and supported by the IASLC Board of Directors, was to set up the Strategic CT Screening Advisory Committee (IASLC-SSAC). The Strategic CT Screening Advisory Committee is currently engaging professional societies and organizations who are stakeholders in lung cancer CT screening implementation across the globe, to focus on delivering guidelines and recommendations in six specific areas: (i) identification of high-risk individuals for lung cancer CT screening programs; (ii) develop radiological guidelines for use in developing national screening programs; (iii) develop guidelines for the clinical work-up of "indeterminate nodules" resulting from CT screening programs; (iv) guidelines for pathology reporting of nodules from lung cancer CT screening programs; (v) recommendations for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening programs; and (vi) integration of smoking cessation practices into future national lung cancer CT screening programs.

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In November 2010, results from the National Lung Screening Trial (NLST), sponsored by the National Cancer Institute (NCI) in the United States, showed that lung cancer deaths fell by 20% and all-cause mortality fell by 7% when smokers—defined as current or former smokers with 30 or greater pack years of smoking—were screened annually for 3 years using low-dose spiral computed tomography (LDCT) compared with standard chest x-ray. The study followed more than 53,000 current and former smokers aged 55 to 74 years. It was halted because the reduction in cancer deaths provided an answer to the study's main question. This announcement by the Director of NCI was significant as it

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demonstrated for the first time in a randomized trial that the early detection of lung cancer could significantly reduce lung cancer mortality. In the wake of this landmark finding, there has been a spirited discussion within the lung cancer community as to how and when CT screening for lung cancer should be implemented into national programs. In parallel, there has been considerable discussion about the potential benefits and hazards associated with the introduction of wide-spread ad hoc commercial screening. Shortly after the NCI Press release on the NLST trial,¹ the International Association for the Study of Lung Cancer (IASLC) Board of Directors requested the Chair of the IASLC Early Detection and Prevention Committee in December 2010 convene a Task Force to develop an IASLC position statement. The Remit of the Task Force was to develop recommendations on (i) the significance of low-dose CT; and (ii) the appropriate work-up for screen-detected lung cancers. The core task force group focused on the former question. The membership of the core task force was based on individuals who were currently undertaking national randomized controlled trial (RCT) screening trials; in addition, expert clinical groups were organized to include international representatives from other spiral CT research groups.

The IASLC CT screening task force concluded that the NLST spiral CT screening trial was the first randomized trial to demonstrate a significant reduction in lung cancer mortality, but there was a range of other published data regarding aspects of optimization of the many components of population-based CT detection of early lung cancer. This innovation provided a great opportunity for lung cancer clinicians and researchers across the world to work responsibly to provide, study, integrate, and refine this new approach within future clinical trials and national screening programs.²

The Task Force's Position Statement outlined a number of the major opportunities to further improve this approach. Based on experience with cancer screening from other organ sites, especially breast cancer, there is a need to introduce quality control measures to ensure the quality of the screening management. The most critical aspect of this is that lung cancer screening should be performed by a multidisciplinary team experienced in evaluation and management of early lung cancer. This involves a number of linked components of optimal care beginning with defining the target cohort, optimizing the image acquisition and interpretation, working up the suspicious nodules, operating safely on the detected cases, and then maintaining ongoing surveillance in an effective and economical fashion. There are a number of trials currently under way that could provide relevant data.³⁻⁵ One of the largest is the Dutch-Belgian-Danish NELSON, a population-based trial of more than 20,000 smokers, which uses standardized, high-resolution CT imaging techniques including the use of change in nodule growth as a filter for selecting clinically aggressive cancers to guide invasive diagnostic work-up.⁶ The ongoing results of the NELSON trial will provide additional information not only on mortality advantage but also on the cost impact of a uniformly applied and optimized approach to the clinical management of lung cancer screening. In light of these positive developments, each

nation will decide how to integrate lung cancer screening into its existing healthcare structure. Given the high mortality of lung cancer with conventional diagnostic approaches, in some national settings, the public may be proactive in seeking access to lung cancer screening services. Although this approach may benefit some, there are also important health risks associated with CT-based screening. Ensuring the dissemination of responsible information to both primary care physicians and patients regarding this new approach will be a critical challenge that must be addressed in a culturally appropriate fashion. The Position Statement stated that to inform the process of implementation of lung cancer screening at a national level, the IASLC will assemble and disseminate information about the relevant evidence regarding the range of specific issues with implementing and optimizing lung cancer screening care:

- i. Define optimal risk populations who will benefit from screening.
- ii. What is the cost-effectiveness of CT screening?
- iii. Harmonization of the CT screening protocols to an acceptable level of consistent performance, utilizing volumetric analysis.
- iv. Define the value of the individual work-up techniques, standardization of performance, and defining appropriate sequence.
- v. Define the optimal surgical management of patients with screen-detected nodules.
- vi. Define the optimal screening interval and the number of screening rounds for both screen-negative and screen-positive individuals.
- vii. Hosting forums to encourage research collaboration around improving screening outcomes while reducing the cost and complications of this management approach.

The recommendation was to support phased, internationally coordinated "demonstration projects," for different geographic regions and in countries that are not currently undertaking large RCTs. A consensus emerged that based on positive reports, smoking cessation programs should be integrated into these CT screening programs. The Task Force was confident that the initial findings from NLST that CT screening save lives would be generalizable. Therefore, subject to national review processes and following the concept of "informed decision making," the recommendation that CT screening could be implemented at national levels is subject to local considerations. This was reflected in the IASLC Position Statement on CT Screening which was published to coincide with the publication of the NLST article in *The New England Journal of Medicine*.⁷ The United Kingdom Lung Cancer CT Screening (UKLS) trial team published a Position Statement with a similar content but with additional recommendations to those who might be considering offering screening in the United Kingdom.⁸

STRATEGIC PLAN FOR PROGRESS

The IASLC CT screening workshop brought together the expertise of radiologists, pulmonologists, surgeons, pa-

thologists, and cancer screening experts across the globe. Most of the participants have been involved in the design and execution of CT screening trials. The combined expertise of this multinational, multidisciplinary group positions the IASLC to take a leading role among professional societies in developing guidelines for CT screening implementation across the world.

A major strategic decision was made to formalize the IASLC Expert Working Groups to serve multiple purposes: (1) to identify and prioritize the remaining unanswered questions about optimal screening technology, assisting with the design of demonstration projects that could address these concerns; (2) to advise on standards for CT screening implementation in collaboration with appropriate professional organizations and accreditation bodies internationally; and (3) to coordinate efforts with other organizations that are contemplating the development of guidelines.

A number of questions remain outstanding and should be prioritized for systematic assessment. Among these are how to define an optimal, standardized definition of screen positivity based on nodule features (diameter and volume) that will maximize specificity. In addition, the resolution of CT screening continues to rapidly improve, which means that the trend to detect even smaller primary lung cancers will continue. This is a positive trend as smaller primary tumors as shown by the IASLC staging data are less likely to be metastatic.⁹ Smaller primary lung cancers may also allow more tailored surgical or other interventions to control the primary tumor to further reduce the cost or complication rate of this management. These evolving management issues are where the IASLC multidisciplinary nature can bring value by sustaining the research environment across its global membership to facilitate such progress.

The Core Task Force and Screening Implementation Group recommended the importance of gathering more data and establishing standards before introducing lung cancer screening to assure optimal outcomes and patient safety. However, clearly there will be variable rates of national implementation of screening across various countries. The Core Group reemphasized the importance of completing the ongoing European CT RCTs. However, RCTs not yet initiated might consider converting to demonstration projects or answering specific screening management questions not yet examined in an RCT.

The following recommendations were made by the Core Task Force and Screening Implementation Group:

- Encourage new screening-related research, i.e., risk stratification, new technology, and biomarkers.
- Quality standards must be developed, endorsed, and embraced before offering screening. Quality standards must be adhered to in organized and individualized settings, with standardized reporting of outcomes and continuous quality improvements.
- Smoking cessation programs should be included in all CT lung screening programs; however, minimal standards for such programs need to be implemented.
- IASLC should partner with relevant organizations to define best practices at this time, disseminate best practices, encourage ongoing research, and screening pro-

grams should monitor and report findings. At this time, there is no common consensus regarding international CT screening quality standards (QA).

- Within the next several months, IASLC should partner with professional societies already developing QA standards and convene workshops to rapidly evolve consensus QA guidelines for lung cancer CT screening which then can be disseminated as soon as possible.
- The IASLC should offer support for information exchange for groups seeking to initiate new screening research studies and demonstration projects.
- The IASLC should explore offering training workshops focused on best practices in implementing and sustaining CT lung cancer screening programs.
- IASLC should promote the concept of multidisciplinary diagnostic coordination, collaborate with professional societies to identify best practices, and disseminate these recommendations.
- IASLC should provide support for a Strategic CT Screening Advisory Committee (SSAC) and the ongoing deliberations of the expert workgroups focused on best practices in the conduct of CT lung cancer screening programs.

DEVELOPMENT OF UNIFORM RADIOLOGY STANDARDS

Establishing the efficacy of low-dose helical CT in reducing lung cancer mortality is a necessary but preliminary first step toward its rational implementation for population screening. The efficacy of CT observed in the NLST was achieved in a controlled setting at sites with medical expertise and resources. It involved standardized processes for image acquisition, interpretation, report communication, and follow-up data collection, had the benefit of diagnostic guidelines developed by radiologists trial-wide, and relied on rigorous end point verification by an independent committee of physicians.^{7,10}

With large-scale implementation, uniform standards throughout the screening process will be imperative. Standardization ensures quality control, promotes the more accurate assessment of the evolution of nodules over time at individual institutions, improves the comparison of results across different institutions and within different trials, and ensures the maximum benefits relative to risks among screenees. These types of quality control measures are being recommended for clinical trials but also are critical in routine healthcare delivery sites to ensure the quality of those processes as well.¹¹ The IASLC Radiology Working Group identified the need for standards in multiple areas:

1. Equipment standards, calibration, and regular monitoring;
2. Uniform acquisition parameters that optimize image quality at minimum radiation doses;
3. Standardized approaches to image and nodule analysis, with attention to software requirements for quantitative analysis;
4. The use of controlled vocabularies to standardize feature analysis, screening interpretations, and communication of results;

5. Standardization of follow-up algorithms;
6. The collection of necessary screening outcomes to monitor and guide screening practices.

The standardization of screening practices will necessarily be iterative and must account for differences in technological resources internationally. A strategic approach to address this is a tiered guideline that defines two levels of standardization: (1) optimal processes, which serve as the benchmark for large-scale screening, and (2) satisfactory processes to accommodate differences in availability of technical resources. A major point of discussion is the approach to nodule assessment. The NELSON⁶ and other screening trials^{12,13} have shown excellent results with the use of nodule volumetry and have validated the higher reproducibility of volumetric measurement and its greater sensitivity to size change relative to manual two-dimensional (diameter) measures. Although not presently feasible in all screening environments, there was wide acceptance among members that nodule volumetry should be the optimal benchmark.

There has been no large-scale project that specifically addresses the overall impact on long-term outcomes of nodule analysis using two-dimensional diameters versus nodule volumetry. Such a demonstration would be important in guiding the directions that should be taken in standardizing nodule assessment over time.

Finally, the large-scale implementation of screening will tax most medical systems. Nodule volumetry software and training of nonphysician image analysts to perform quantitative image analyses may be essential to the feasibility of high-risk population screening. The IASLC Radiology Working Group will develop imaging standardization consistent with best practices for both manual two-dimensional and semi-automated three-dimensional quantitative assessment as well as other discriminating features of nodule characterization.

DEFINING SCREEN POSITIVITY

A major challenge of LDCT screening is the high false-positive rate, which exposes screenees to unnecessary, potentially deleterious diagnostic evaluations and psychological discomfort. The definition of screen positivity represents a compromise between high sensitivity (fewer missed cancers) and high specificity (fewer false-positive screens). In the NLST, screen positivity was defined by greatest nodule diameter of 4 mm or larger.¹ Overall, 24% of all CT screens were positive using this definition. In contrast, the NELSON trial based screening interpretation on nodule volumetry and used a tiered approach. They classified nodules less than 50 mm³ (4.6-mm diameter) as negative, nodules greater than 500 mm³ (>9.8-mm diameter) positive, and nodules 50 to 500 mm³ indeterminate. Indeterminate nodules underwent an early (3-month) follow-up LDCT to assess for growth; nodule volume doubling times were then used to distinguish between positive screens requiring additional diagnostic procedures and negative screens.⁶ Using this two-step approach, 2.6% of NELSON baseline screens were positive, and a higher proportion of positive screens were due to lung cancer.

The use of nodule volumetry mandates that image acquisition provides isotropic datasets of high spatial resolu-

tion while minimizing physiologic motion. In the NELSON, image datasets were acquired using 16-detector row scanners at 1 mm thickness with 0.7 mm overlapping reconstruction. The volumetric software (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions, Erlangen, Germany) is one of several commercially available and can be used with CT data in DICOM format from any scanner platform.¹¹ In a sample of nodules of varying size, these investigators have observed high interobserver correlation ($r = 0.99$) with discrepant results seen in 10.9% of cases, typically amounting to less than 10% discrepancy. Discrepancies are most common with very small nodules (<30 mm³) because of volume averaging effects in which the outer voxels of the nodule fall outside the threshold for analysis and in larger nodules with irregular shape, irregular margins, or spiculation.^{14,15}

Using volumetric analysis to define positivity as an increase in nodule volume of at least 25% between two scans in nodules between 50 and 500 mm³, the NELSON trial reported a screen sensitivity of 94.6% (95% confidence interval [CI]: 86.5–98.0) and a negative predictive value of 99.9%. The performance characteristics of screening CT in the NLST have not yet been reported.

Ground-glass nodules (GGN) pose unique problems for assessing evolution, as volume growth may be subtle. The notion of nodule “mass” has been proposed, in which nodule evolution (growth) is based on changes in the product of nodule volume and average density. The measure of mass is more sensitive to the development of solid components in GGN, which are known to be highly associated with malignancy.¹⁶

The mortality results of the NELSON trial are pending, but the unique methodological features of this randomized trial have yielded important insights that complement the information gained from NLST. Volumetric analysis promises greater reproducibility and accuracy in nodule characterization. It will fall to the individual medical communities to determine whether the performance improvement using nodule volumetry outweighs the inevitable alterations in radiologist workflow and incremental costs of dedicated analytical workstations, software, and staff. Alternatively, there may be technological innovation related to host web services that could emerge as a reference resource in providing support to volume analysis approaches, and this is an area where further research should be encouraged.

MULTIDISCIPLINARY TEAM WORK-UP OF POSITIVE CT-SCREENED NODULES

The pulmonary group supported the concept that cohorts with high risk of developing lung cancer may be offered screening as already discussed. This approach has been used in the UKLS trial¹⁷ where the Liverpool lung project risk prediction model is used to select high-risk individuals.¹⁸ When a suspicious nodule is found based on a priori defined criteria, that case should undergo subsequently follow-up to assess for growth. Cases that demonstrate significant nodule growth should be referred to a multidisciplinary group with expertise in lung cancer for further work-up. It was noted that only those who are at a high risk of developing lung cancer

should be offered screening and so when a nodule is found, criteria for a positive result should be predicated on this. The pulmonology group agreed with current standards that nodules smaller than 4 to 5 mm in diameter (or equivalent volume) should be followed up on their first annual repeat screening. For larger nodules, where additional work-up is recommended in a shorter time frame, there will also be some size cutoff where these should be referred directly to the multidisciplinary group. The suggestion was that 8 mm constituted a reasonable threshold. Size criteria for both a positive result and referral to the multidisciplinary group will be further refined by analysis of data from various research groups that have already amassed large databases of nodules with their attendant outcomes. The aim of this analysis will be to optimize the specificity/sensitivity characteristics of the screening process. This will entail establishing the size (and other nodule characteristics) that will minimize both the number of cases requiring additional work-up and the number of cases of cancer that are classified as a negative screen at baseline, while minimizing the occurrence of interval-detected cancers. The ground-glass (nonsolid) nodule was recognized as being particularly promising in terms of redefining the size cutoff for a positive result as it is recognized that they are particularly slow growing and when diagnosed as cancer, highly amenable to treatment.

Among those abnormalities not meeting the criteria of positive result, the recommendation for annual repeat screening is advised although additional considerations may alter this as new data emerges. In this situation, the results do not need to go to the multidisciplinary team and can be referred to either a nurse or primary or secondary care physician to continue screening at appropriate time intervals.

The work-up algorithm for nodules above the threshold size for being considered positive will also have management determined largely by size criteria. Growth assessment will remain a key determinant of the work-up, and definitions as to what constitutes true growth are being formulated. The relationship of initial size of nodule to the interval between baseline and repeat scan is also uncertain and will be informed by analysis of existing data. Once interval primary tumor growth is established, further evaluation with either positron emission tomography CT or tissue sampling may be useful. Tissue sampling will depend on a number of factors including the patient and nodule characteristics and local expertise in performing these procedures. For tissue sampling, bronchoscopy with navigation techniques is now emerging as a useful approach (for larger nodules) along with transthoracic core needle biopsy and thoracoscopy. To determine the relative utility of bronchoscopic compared with percutaneous CT-directed biopsy approaches is an important research question, particularly to determine the safest, most effective, and most economical approach to diagnostic work-up. There may also be some threshold size (10–15 mm) where a decision to go directly to tissue sampling may be reasonable. Defining the actual size threshold constitutes another important area for research. The molecular characterization of tumors detected by CT screening compared

with clinically detected tumors is another area of interest for future research.

As with any screening approach, participants enrolling in a lung cancer screening trial should have a baseline level of fitness that will allow them to benefit from early detection and treatment of lung cancer. This should include generally healthy, asymptomatic individuals with a willingness to undergo treatment if necessary and an approximate 10-year life expectancy. Various risk assessment models and algorithms for patient fitness may have an important role in deciding eligibility for enrollment into a screening program.

SURGICAL ASPECTS OF THE IMPLEMENTATION OF CT SCREENING

A major risk factor in CT screening is the large number of indeterminate pulmonary nodules that will be detected and may require diagnostic interventions. In the NLST screening trial, at prevalence screen, the false positivity rate was found to be more than 95%.⁷ Inappropriate surgical interventions may put the screened population at risk, to a much higher degree than in other cancer screening programs, because the surgery itself carries a higher risk. However, well-performed surgery may often offer the best chance of early diagnosis and cure for this otherwise lethal disease. It is essential that surgeons undertaking treatment and diagnostic procedures in a screening setting are sufficiently qualified and prepared for this task.

The Surgical Expert Group proposes specific requirements for future lung cancer screening trials. Surgeons should be involved in the set up and design of any future screening or demonstration programs as well as in the diagnostic process as in the multidisciplinary meetings. This group also considered it was important that the surgeon be experienced in thoracic surgery and in evaluating pulmonary CT scans. It is strongly recommended that surgery be performed in centers with access to a full minimally invasive surgical program, including the ability to perform video-assisted thoracoscopic surgery (VATS) anatomical resection when appropriate. Robotic surgery with lobectomy is at present under development and may be an option in some centers. This group recommended that a formal protocol for the diagnostic and surgical management be prepared.

Surgical participation in work up of detected nodules was based on the workshop recommendations from the Expert Radiology Group. In screenees with indeterminate nodules, the purpose of the surgical diagnostic intervention is to obtain pathological proof of the character of the nodule. The decision to go ahead with surgery depends on many factors including number of nodules, patient condition, and comorbidity. Several radiological diagnostic guidelines exist including those proposed by the Fleischner Society in 2005,¹⁹ the American College of Chest Physicians,²⁰ from Japan,²¹ and from Italy.²² This is a crucial area for further research, as the clinical management of suspicious nodules will greatly influence the efficiency and cost of the overall screening process. Although demonstration of primary tumor growth is emerging as a promising approach to minimize overdiagno-

sis, the definitions vary as to what constitutes significant growth and how to manage the consequences of those measurements. Volumetric evaluation used by NELSON seems to be more precise and results in low number of false-positive test results (1.8–3%).⁶ Nodule volume doubling time less than 400 days has been proposed as an indication of malignancy and for surgical exploration.⁶ The UKLS have recently published the nodule management protocol which will be used in the United Kingdom, which has used many of the NELSON principles.¹⁷ There is an urgent need for harmonization of radiological guidelines.

The Surgical Group was of the opinion that the use of CT-guided biopsy for suspicious nodules should be encouraged and will in many cases facilitate the surgical decision process.^{23,24} The involvement and expertise of interventional radiologists or pulmonologists specialized in minimally invasive biopsy using percutaneous, navigational bronchoscopy and endobronchial ultrasound techniques are important. Further research to define a potential role for positron emission tomography in characterization of small pulmonary nodules is a near-term opportunity.

The surgical techniques used for excision of indeterminate nodules will most often be a minimally invasive wedge resection depending on the location and the size of the lesion. With small primary lung cancers, thoracotomy will be required less than in the past. The natural history of small nodules below 10 mm and especially ground-glass opacity lesions is not yet fully defined. In addition, it may be difficult to locate such small primary tumors for excision. Therefore, the experience of the surgeon in primary localization is important and subject to further research, and longer observation time may be justified until growth is unequivocally established. Methods for the location and marking of small nodules are still cumbersome and not widely used. Improved technology in this area could have a great impact on patient management and safety.²⁵ When a diagnosis of lung cancer is known or suspected preoperatively, the preoperative investigations follow standard guidelines according to tumor, node, metastasis staging and condition of the patient.²⁶

Surgical treatment options were also considered by this Expert Group. In general, anatomical resection by lobectomy with systematic nodal dissection is the recommended treatment. Reports from Society of Thoracic Surgeons and other groups have been published evaluating video-assisted surgical approaches compared with open thoracotomy to managing small primary lung cancers with favorable results.^{27–29} For small peripheral lung cancers below 2 cm, more limited surgical approaches are being studied in two ongoing randomized clinical trials. In the United States, the CALBG trial (CALBG1140503 protocol) compares wedge and anatomical segmental resection with lobectomy. The Japanese Clinical Oncology Group trial compares segmental resection with lobectomy.²⁷ However, the result of these trials will only be available in 5 to 10 years time. However, until then, it is recommended that anatomical segmentectomy be reserved for the CT screening-detected pure ground-glass opacity lesions or part-solid lesions below 2 cm located in the peripheral third of the lung, after frozen section of N1 and N2

lymph nodes have confirmed the T1aN0M0 status. In addition, frozen section or cytological evaluation of resection margins is recommended.

Patients with reduced pulmonary reserve or multiple lesions requiring excision are also suitable for segmental resections, even for solid lesions. Minimally invasive surgical techniques by qualified surgeons are strongly recommended.

HANDLING OF PATHOLOGY SPECIMENS FROM CT-SCREENED PATIENTS

Increased use of CT screening for lung cancer will greatly impact the number and type of pathology specimens. The following comments are directed at lung cancer specimens and do not address issues related to the “false positive” situation where a benign diagnosis is obtained.

As CT-guided preoperative biopsies will play an important role in evaluation of CT-detected lung nodules, official guidelines for diagnostic terminology and criteria for lung cancer diagnosis based on small biopsies and cytology were recently provided by the 2011 IASLC/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification.³⁰ Although 70% of lung cancer patients overall present in advanced stages,³⁰ in CT-screened lung cancers, approximately 20% are advanced stage (stages IIIB and IV) and 80% are resectable (stages I–IIIA).⁷ In experienced hands, a fine needle biopsy can be used to evaluate a screen-detected nodule with sensitivities up to 90%. The availability of an on-site cytologist or pathologist can be helpful but it is not essential.

For resected lung cancers, pathology specimens should be processed according to established protocols.³¹ Tumors should be classified according to established pathologic criteria such as the 2004 World Health Organization classification³² and 2011 IASLC/American Thoracic Society/European Respiratory Society adenocarcinoma classification.³³ In the new lung adenocarcinoma classification, there are several major conceptual changes that have important implications for pathologic processing of early lung adenocarcinomas that are likely to be detected by CT screening. First, the term bronchioloalveolar carcinoma is no longer used. For the early adenocarcinomas that were previously classified as bronchioloalveolar carcinoma, there are three newly defined entities that are likely to correspond to small solitary tumors that by CT appear as pure GGN or part-solid nodules with a predominant ground-glass component.³⁰ These include adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and lepidic predominant adenocarcinoma. AIS and MIA are small solitary ≤ 3 cm tumors that should have a 100% or near 100% 5-year survival, respectively, if completely resected. AIS have pure lepidic growth without invasion, and MIA is a lepidic predominant tumor with ≤ 0.5 cm invasive component.^{33,34} Lepidic predominant adenocarcinomas have a predominant lepidic growth pattern with more than 0.5 cm of invasive component, and these may be larger than 3.0 cm. Five-year disease-free survival for resected tumors is approximately 90%.³⁴ It is also hypothesized that the size T factor may be better assessed by measuring invasive size rather than total size including the lepidic

component. This may be applicable to CT assessment of tumor size for clinical staging with GGN or part-solid nodules. Potentially, AIS may be classified as Tis (adenocarcinoma) and MIA may be Tmi. However, this is a proposal that needs to be validated in multiple radiologic and pathologic datasets, before it can be officially adopted by the Union Internationale Contre le Cancer/American Joint Cancer Committee tumor, node, metastasis classification.

THE ROLE OF INDUSTRY

A major requirement for large-scale screening implementation is the availability of commercially available screening management systems that expedite and standardize reporting, reminders, the documentation of screening results, and recording results of downstream diagnostic tests in a database that can be readily interrogated. The Radiology Committee identified the development of screening management systems as a major need and opportunity for industry to collaborate with qualified institutions to understand workflow, standards, and data elements that form the blueprint for such management systems.

Similarly, a critical need for industry is the availability of image datasets acquired at high (isotropic) resolution across all commercial CT platforms that can be used to validate analytical software for nodule volumetry and feature extraction. Datasets that provide a standard of truth against which commercial software can be tested as well as “coffee break” imaging exams to measure repeatability should be goals of multinational collaborations moving forward. An example of this is the recent effort by Oxnard et al. in which they performed comparative radiological analysis in a series of “coffee break” cases and then made those DICOM files available for further research through the NCI’s website.^{16,28,29,35} The routine donation of image files from screening research studies is a practice that the IASLC has to strongly encourage to allow more rapid progress in this new but promising area.

THE ROLE OF STANDARDIZATION IN SCREENING IMPLEMENTATION

The widespread implementation of LDCT screening for lung cancer can borrow lessons from the implementation of breast cancer screening^{36,37} but will also impose significant new challenges. For the imaging community, LDCT screening will require a high standard: sophisticated multidetector CT scanners and analytical software, professional physicists, and staff who can certify equipment and perform studies to a consistent standard at acceptable radiation exposures, ongoing imaging quality assurance,³⁸ qualified radiologists who use controlled terminologies and standardized interpretation guidelines, reliable communication requirements with primary care physicians, medical environments that can absorb patients who require ongoing management, and the responsibility of tracking screened individuals and documenting outcomes.

CT screening benefits outweigh risks in the setting of high-risk cohorts, but its cost-effectiveness must be quantified. Cost-effectiveness analyses of CT screening have been

modeled by different groups and have reached varying conclusions.^{39–42} A formal cost-effectiveness analysis from a societal perspective is also in progress using NLST data that will compare CT screening with chest radiography and no screening across time horizons both within trial and lifetime. This analysis will be fundamental to future guidelines development. Depending on the results of such analyses, primary providers may be challenged to agree that LDCT screening is a health priority to tolerate disruption of normal workflow, and to divert time, resources, and patient education from other evidence-based preventive measures. For the public, the challenges will be the equitable implementation of screening across all socioeconomic strata at risk. This is particularly important for lung cancer, in which a disproportionate burden of the disease affects individuals in disadvantaged communities, often because of lack of awareness of lung cancer risk, financial limitations, fears of radiation and other screening-associated interventions, and the unique cultural concerns of trust, fatalism, and stigmatization associated with medical screening and practice.^{43–45}

The efficacy of CT screening can be greatly enhanced if positioned in multidisciplinary programs that offer comprehensive coordination of care between primary and subspecialty providers and in which aggressive smoking cessation programs are readily available. CT screening provides a potentially teachable moment for smoking cessation but should be further advantaged to sustain smoking abstinence long term.^{46–48} If achievable, CT screening, smoking cessation, and ultimately chemoprevention opportunities in high-risk smokers could dislodge lung cancer from its current position as the primary cancer killer to a curable disease.

It was concluded that only through rigorous quality control and follow-up would we attain the best results from CT screening programs. The Expert Surgical Group made a very clear recommendation that all surgeons involved in screening programs should be qualified in chest surgery, in particular that the surgeons performing VATS surgery should have performed at least 15 VATS lobectomies independently. The IASLC could work with other professional societies to evolve a training program to keep clinicians abreast of the fast-moving developments for lung cancer screening management and to ensure all clinicians are trained on new clinical management techniques. The outcome of all surgery should be monitored with regard to mortality, morbidity, and nodal evaluation, in addition to the conversion rate to thoracotomy during VATS surgery. Surgeons should minimize the number of resections for benign disease (based on the data that is available from trials to date, this should be below 15%). To achieve this objective, it is recommended that the formal protocol and guidelines for the surgical management are adhered to within a multidisciplinary environment and that outcomes on these parameters are shared with the public so that high quality of care is maintained.

At national levels, there should be systematic registration and documentation of all screening-related lung cancer cases in a formal database, as well as all screening-related surgery and other participant-related interventions.

The end goals of lung cancer screening are to reduce the morbidity and mortality of lung cancer. We are at the cusp of implementation; improvements in screening will necessarily require a systematic, multifaceted approach across multiple medical disciplines. The complementary use of molecular biomarkers to identify those at risk who should undergo screening or more aggressive diagnostic strategies for positive screens is considered achievable in the near future.

Optimal practices for the community, the primary setting, and screening programs can only be understood and measured through funding for demonstration projects, which must be a critical priority in order for lung cancer screening to be rapidly and successfully implemented.

FUTURE PRIORITIES

The IASLC Board of Directors has agreed to set up the SSAC. The SSAC is currently engaging professional societies and organizations who are stakeholders in lung cancer CT screening implementation across the globe to focus on delivering guidelines, and recommendations in six specific areas:

1. Identification of high-risk individuals for lung cancer CT screening programs.
2. Develop radiological guidelines for use in developing national screening programs.
3. Develop guidelines for the clinical work-up of “indeterminate nodules” resulting from CT screening programmers.
4. Guidelines for pathology reporting of nodules from lung cancer CT screening programs.
5. Recommendations for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening programs.
6. Integration of smoking cessation practices into future national lung cancer CT screening programs.

IASLC recognizes the importance of engaging the major international stakeholders in lung cancer CT screening to develop these guidelines and recommendations and is currently taking this initiative forward.

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