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Lung Cancer Workshop XI: Tobacco-Induced Disease: Advances in Policy, Early Detection and Management: Meeting Report

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Abstract

The Prevent Cancer Foundation Lung Cancer Workshop XI: Tobacco-Induced Disease: Advances in Policy, Early Detection and Management was held in New York, NY on May 16 and 17, 2014. The two goals of the Workshop were to define strategies to drive innovation in pre-competitive quantitative research on the use of imaging to assess new therapies for management of early lung cancer and to discuss a process to implement a national program to provide high quality CT imaging for lung cancer and other tobacco-induced disease. With the central importance of CT imaging for both early detection and volumetric lung cancer assessment, strategic issues around the development of imaging and ensure its quality are critical to ensuring continued progress against this most lethal cancer.

Integration of Quantitative Imaging into Lung cancer: Keynote address: Bringing Precision Quantitative Imaging to Manage Major Chronic Diseases

In his overview remarks, Dr. Mulshine outlined that The Prevent Cancer Foundation has sponsored a lung cancer quantitative imaging workshop since 2004, in which the faculty jointly considers how to more rapidly advance the application of quantitative CT imaging in the management of early lung cancer. (1) At the onset of this Workshop series, it seemed highly improbable that on Dec 31, 2013, the United States Preventive Services Task Force (USPSTF) would make a final recommendation for the use of spiral CT in the early detection of 55-year-old and older, ever smokers as an evidence-based recommendation. (2)

From a screening implementation perspective, the other remarkable development was the provision in new federal legislation (the Affordable Care Act) requiring every commercial payer to implement a plan for the delivery cancer screening service recommended by the USPSTF, without any co-pay, as aroutine service. (3) Due to the confluence of these two events, at the 11th Prevent Cancer Foundation Workshop, Tobacco- induced Disease: Advances in Policy, Early Detection and Management, we are on the brink of national implementation of low-dose CT cancer screening.

The issues surrounding the national implementation of low-dosed CT emerged as the central focus of Workshop. The workshop steering committee's technical experts included David Yankelevitz, an early proponent of applying quantitative imaging to lung cancer management; Thomas Baer, a pioneer in the biomedical applications of optics; Rick Avila, an early and highly productive contributor to quantitative imaging and the open source imaging field; and Raul San Jose Estépar, an expert on quantitative techniques for CT assessment of COPD and other forms of lung injury. The steering committee also included two internationally prominent leaders in patient advocacy, Carolyn Aldigé of the Prevent Cancer Foundation and Laurie Fenton Ambrose of the Lung Cancer Alliance.

The goal set by the Committee was to convene a highly interactive forum of leaders to outline key technical priorities in improving the quantitative imaging process for managing early lung cancer, with the goal of reducing its mortality burden. A distinctive aspect of this forum is that a parallel goal was to formulate a way forward for the early lung cancer detection process from a health policy perspective. The dialogue between experts in technical quantitative imaging issues with experts in health policy created a challenging but critical conversation since these two divergent fields rarely have occasion to otherwise interact.

In this forum, we also have been reviewing progress with the application of quantitative imaging to not only detect early lung cancer, but also to evaluate early coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD). LDCT is emerging as an informative biomarker of these other two frequent complications of tobacco exposure. The goal is to leverage the full thoracic imaging information acquired in the course of performing a LDCT screening not only about lung cancer but also about the status of the coronary arteries as well as lung parenchymal injury. This more comprehensive information could enrich the dialogue with lung screen screening subjects regarding other possible sites of tobacco-related thoracic disease risk as this additional imaging data is available without additional cost and enhances the efficiency of this large new screening investment.

Quantitative Lung Imaging and The Radiological Society of North America (RSNA)

The Workshop has been successful in advancing the dialogue on how to best integrate quantitative imaging into early lung cancer in large part due to collaborations with other professional organizations that share an interest in the field of quantitative imaging including the RSNA. (4) This year the keynote address, entitled “Bringing Precision Quantitative Imaging to Manage Major Chronic Diseases,” was given by Dr. Dan Sullivan

who chairs the Quantitative Imaging Biomarker Alliance (QIBA) of RSNA. In his presentation, Dr. Sullivan emphasized two key factors: “consistency,” reflecting the need for standardization, and the challenge of “false positives,” indicating the need for objective interpretations. Neuroimaging as conducted by the Alzheimer's Disease Neuroimaging Initiative (ADNI) was presented by Dr. Sullivan as an example of an inclusive collaborative public-private partnership between investigators and the Institute of Medicine to develop a forum to address relevant issues in an ongoing process. (5) He then pointed out that variance in clinical medicine leads to less favorable clinical outcomes and that precise quantitative imaging is a potential solution to address this problem. To explore this opportunity in 2007, QIBA was formed to catalyze the process of “industrializing” imaging biomarkers.(6) The criteria that QIBA employs for selecting imaging biomarkers to work on include whether the biomarker is transformational, which implies addressing a significant medical need, as well as its likelihood of resulting in significant improvement in the development, approval, or delivery of care to patients. Another major selection factor is whether the biomarker is feasible and the end goals can likely be achieved in a specific time frame. A related factor is whether the biomarker is practical, meaning it leverages preexisting resources (e.g., workflows, personnel, facilities, specimens, reagents, and data) wherever possible and therefore warrants access to RSNA resources and support. A key strategy for this QIBA effort is to accelerate progress by routinely collaborating with other relevant partners with content expertise in the specific area of care.

Methodological Issues with Quantitative Imaging

Spiral CT is one of the key modalities for quantitative development with QIBA, since the CT signal is linearly proportional to density and has particularly favorable spatial resolution characteristics so it can be quite accurate for distance measurements. The approach that QIBA has developed entails a four-stage process, including identification of sources of error and variation, evaluating specific solutions to overcome the challenges, and then codifying those solutions in the form of a narrative process document that is called a “QIBA Profile”. The performance of the proscribed Profile process is then formally tested and the key components of the solution are promulgated as a “profile” for vendors and users: first, minimize image acquisition variability, outline factors for the radiologist to reduce reader variability and then finally minimize measurement methods variability. (7)

To make progress on the goals of QIBA, it has been necessary to define new methodologies for rigorous assessment of lesion volume quantitation. A recent supplement contains a series of papers that discuss a number of complex but critical issues involved in these analyses. This supplement is entitled, “Developing Metrology Standards for QIBA: Terminology, Technical Performance, Algorithm Comparisons” and this issue is in press in the journal Statistical Methods in Medical Research. The editors of this landmark issue are Drs. Nancy Obuchowski, Larry Kessler and David Raunig. The output of all of this work is to more clearly define the validation process. For example in a profile document the steps necessary to perform a quantitative image study are defined in a step-wise fashion. The expectation is that if the profile steps are carefully followed then a “claim,” statement would relate of how reliably precise and consistent the volumetric image measurement is likely to be. (8, 9)

A number of research projects have been funded by QIBA to sort out complex issues with regard to defining the expected amount of variance with imaging volume measurement. At this stage in the development of the field, this has involved working with phantoms and synthetic digital reference objects to enable an objective source of ground truth for accurate volume measurement. The goal of QIBA is to demonstrate actual improved clinical measurement precision through deployment of its protocols.

Much of the discussion during the workshop focused on the specific use-case of moving LDCT screening forward now that the USPSTF has recommended this early cancer detection tool. Moving this service into the realm of routine clinical care, so that it is readily available at high quality across the nation, is a foundational challenge for quantitative imaging. Having the conditions established so that measurement of pulmonary nodules can consistently be performed with acceptable variance across all different types of CT scanners remains an open challenge and there is much intense interest in this particular issue.

How Quantitative Imaging Can Impact Screening Management

Claudia Henschke of Mt. Sinai discussed an example of how lung cancer screening management improvement could evolve using “big data”. In a recently published analysis, Henschke used screening outcomes of 22,000 screening subjects to explore the likelihood of being diagnosed with lung cancer as a function of the size of the first pulmonary nodule detected by LDCT screening. The conclusion of the analysis is that the diagnostic work-up efficiency could be improved by moving from a smaller size threshold for diagnostic work-up (5 mm) to a larger threshold such as > 6mm. (10) The validity of this approach was confirmed, using the released data from the NLST which demonstrated a similar improvement in reducing the frequency of non-productive diagnostic work-up by using a 6mm nodule size threshold for diagnostic work-up rather than the 4mm threshold used in the NLST. (11)

Status of Harms Reduction: Dose Minimization

The image processing approach, iterative reconstruction was presented as a software development to discriminate critical image signals from background noise to improve the process of lung cancer screening. (12) A critical aspect of iterative reconstruction approaches is the potential to reduce the average medical radiation dose required for a quality LDCT by up to 80% compared to the exposures used in the NLST. (13) However, further research is required to fully understand how this tool can be best applied within the complex setting of lung cancer screening without confounding consistent image quantitation.

A focus of the Workshop was a discussion on how to best capture the useful screening data for re analysis such as with developing a screening imaging registries to monitor quality assurance of this cancer detection service. It was recognized that a model for quality monitoring comes from the American College of Radiology where there is a program to monitor CT scan dose. (14) The system involves having de-identified data sent to a central repository where it is analyzed and reports are sent back to individual sites that provide summary dose reports as well as comparisons to other facilities. It was also recognized that

the opportunity will exist to go beyond reporting parameters that can be extracted from the DICOM (Digital Imaging and Communications in Medicine) files which are the standard format for digital image storage for medical images. The opportunity exists for re analyzing the original clinical image data directly using software that can characterize actual image quality or other relevant features. In this way, a more comprehensive quality assessment can be provided or new image analysis tools can be validated using collections of serially acquired DICOM image files with known clinical outcomes. In light of such opportunities, it was also recognized that standard measures of CT image quality will continue to evolve and there is a need to develop newer metrics beyond those traditionally measured such as noise or resolution. Overall, the Workshop concurred on the idea to develop a large, easy-to-use quality assurance registry including a large number of clinical images files with ongoing meta-data. With appropriate regulatory compliance, this reference image data set should be made available to catalyze image quantitation and related screening process research. This resource was considered to be vitally important to the success of screening and that the I-ELCAP research model represents a model for how such a registry can be developed.

What is the Precision of Current Lung Cancer Screening Quantitation?

A pressing technical issues relates to quantitative imaging relative to lung cancer screening is precise measurement of small pulmonary nodules. Volumetric change percentage thresholds are critical when assessing if a solid lung lesion is changing size when assessment for malignant potential. Mr. Rick Avila presented an analysis of underlying mathematical models combined with verification using several lung cancer imaging datasets was used to arrive at minimum volumetric change recommendations for different ranges of lesion diameters. Specifically, the following volumetric change percentages are likely to exceed known sources of change measurement variation between two consecutive volumetric measurements for solid lesions:

Lesion Diameter=D	Volumetric Decrease %	Volumetric Increase %
5mm <= D < 8mm:	-85 %	+110 %
8mm <= D < 11mm:	-32 %	+ 35 %
11mm <= D < 14mm:	-21 %	+ 23 %

These preliminary findings were presented with the goal of making further refinements in preparation for utilization in the small nodule QIBA profile and other lung cancer CT imaging guidance documents. One of the technical acquisition issues of concern for nearly all current CT scanners is the low axial in-plane sampling rate (i.e. “matrix size”), currently supported with 512x512 pixels per image. Mr. Avila proposed that CT scanner manufacturers support an additional matrix size of 1024x1024 pixels per acquired CT image, which would allow for significant improvement in detection and measurement performance.

Future Advances: Assessing Other Thoracic Structures While Screening

An important emerging question in this regard is whether the conditions to permit optimal lung screening imaging are also optimal to evaluate other organ systems that are included in the field of view on the lung cancer screening image. In the course of lung cancer screening

evaluation of coronary artery calcium, COPD, and breast cancer is possible. However the image resolution for certain of these evaluations may not be sufficient.

An example of where concern for optimal imaging acquisition parameters in lung cancer screening is with quantitative CT assessment for the presence or progression of early COPD in this heavily smoke-exposed population. A major resource for answers in this regard is the consortium funded by the National Heart Lung and Blood Institute conducting the COPDGene Project. (15) In his overview Dr. Raul San Jose Estépar commented on imaging approaches used to quantify disruption in lung structure (parenchyma, airways and vasculature) and outlined which of these measurements be assessed by the imaging technique routinely used LDCT.(16) He also pointed out how COPD outcomes mirror the severe morbidity and mortality experienced with lung cancer, so these are important analyses to perform jointly.(17) Moreover, he demonstrated how quantitation of other structures such as the pectoralis muscle is a more informative biomarker than body mass index for outcomes with pulmonary diseases (18); thus, quantitative CT can bridge the gap between morphology and clinical function for tobacco- related lung disease. This research suggests that information from LDCT screening has significant potential to also inform about the risk of premature death related to COPD in addition to lung cancer.

In a provocative presentation, Dr. Harvey Hecht revealed that imaging coronary artery calcium (CAC) with a dedicated CT study correctly reclassifies 25% of all patients and 67% of intermediate risk patients as determined by Framingham Risk Scores; therefore, coronary artery calcium is considered a most informative clinical risk prognosticator. Dr. Hecht outlined that the target high-risk population for LDCT overlaps with the target population at-risk for atherosclerotic disease. Moreover, based on early studies, coronary calcium analysis done on LDCT, including gated and non-gated measures, is highly correlated with results from dedicated standard dose coronary artery calcium scoring. Hecht reviewed the important technical differences between the different approaches to image acquisition and scoring methods and suggested that the LDCT study can be adapted to perform an informative CAC study within the boundaries of currently acceptable image acquisition protocols. Results from studies comparing the use of iterative reconstruction techniques that can greatly lower the required medical radiation dose as well as newer model-based techniques and the issues in validating these dose reduction techniques were discussed. (19) Currently, the dose required for lung screening is lower than that of CAC screening and the challenge remains on developing a comprehensive approach to optimizing integration into a single protocol. This integration of lung cancer and atherosclerotic disease imaging has the potential for significant public health benefit if these analyses can be performed jointly with acceptable radiation exposure and reliable results.

A new opportunity to maximize clinical information from LDCT emerges with the evaluation of breast density as presented by Dr. Laurie Margolies. As the breasts are routinely included in the field of view in the course of a LDCT, the opportunity exists to analyze that information without incurring any additional medical radiation, imaging time or cost. As more women are screened for lung cancer, there is an opportunity to understand the potential complementary contribution of this imaging study compared with mammography and to integrate this information into a comprehensive program for breast health. A

preliminary study was discussed that highlighted the importance of measuring breast density and demonstrated the correlation between scoring using LDCT compared with mammography. (20) It showed highly favorable results and in addition demonstrated the potential for automated computer-assisted methods. Further research on CT-derived imaging information such as with breast density assessment is an important opportunity.

Dr. Tom Baer from Stanford University reviewed the status of quantitative imaging methods in areas other than with CT lung imaging. This presentation included imaging based on dynamic morphology measurements, i.e., measurements involving extracting key features derived from high resolution 2D and 3D images taken at multiple time points. He highlighted examples from the fields of cancer, neuroscience, and in vitro fertilization. These applications of quantitative dynamic imaging face similar challenges to those encountered with applying quantitative analysis for lung cancer screening management: generation of very large data sets, the need for development of feature extraction software, and ensuring the reproducibility of quantitative imaging data across different platforms and at different time points. Solving these problems requires the assembly of highly skilled, multidisciplinary teams working collaboratively employing many of the development strategies being discussed for lung cancer screening research.

Other Applications of Quantitative Imaging in Lung Cancer Management

The evolution of lung cancer surgery has been remarkable. Dr. Nasser Altorki outlined the progress from extensive resection of an entire side of the lungs for more advanced symptom-detected lung cancer to the more tailored, endoscopic-mediated limited resection frequently done for the smaller, earlier stage, screen-detected lung cancer. (21, 22) As a result of this transition, there has been a significant reduction in surgical complications which includes parameters such as lower rates of atrial arrhythmias, lower re-intubation rates, reduced need for blood transfusion and shorter duration of chest tube drainage as well as decreased length of hospital stay. The smaller primary lung cancers found with screening may allow even more limited surgical procedures to be employed and early pilot experience with these approaches, as well as alternatives to surgery, including limited radiation therapy, are associated with even fewer complication rates. These developments are critical to improving the benefits/harms considerations with lung cancer screening as the field moves forward.

Just as the size and disease extent change the surgical approaches to managing screen-detected lung cancers, there are comparable opportunities to re-engineer the approach to drug management in this setting. Dr. Natasha Leighl outlined options with pre- or post-operative chemotherapy and preoperative window studies. These approaches would also involve in vitro drug selection based on molecularly directed companion diagnostics that are currently uses in selecting the appropriate targeted therapy in advanced stage lung cancer. This is especially attractive for using molecular profiling to align the appropriate drug with the actual tumor resected from an early stage screen-detected cancer patient. Molecular tools can also be used to analyze tumor tissue to determine risk profiles beyond the usual clinical features and suggest who may benefit from exposure to specifically targeted adjuvant therapies as is commonly done with the management of early stage breast cancer. Dr. Leighl discussed the experience to date with neoadjuvant window trials, which provide an

opportunity to assess how a patient is responding to a short course of drug administration. In this study design in consenting patients, an experimental drug is given for several weeks prior to surgery. (23) Images and tumor tissue are compared from before and after the period of drug administration to understand what mechanistic impact the new drug is having on the cancer. This approach is particularly informative since the response to the drug can be matched to the actual status of the tumor's cellular machinery. This gives the researcher much more granular information about the utility of a drug in this clinical setting and this approach could inform the selection of drugs for complementary therapy of early lung cancer such as with screen detected lung cancer or with adjuvant or chemopreventive drug approaches.

Cost Implications of Quantitative Imaging

In considering the implementation of a new clinical service, a fundamental issue is the cost of delivery. Bruce Pyenson, a principal actuarial at Milliman has been working on this question and reviewed the status of his current findings.(24) In summary, an actuarial analysis of actual cost of screening services based on current relevant CPT codes, shows that LDCT screening done in a fashion consistent with an I-ELCAP or NCCN protocol will result in relatively modest cost to Medicare of ∼ $1 per member, per month (PMPM) in 2014 dollars versus ∼$750 PMPM for the full average cost of Part A and Part B. With that cost structure, the additional expense of implementing lung cancer screening - if the rate of uptake of this service by the public is similar to the participation rate with colon cancer screening - will be about $700 million for the first year of national implementation of LDCT screening (with the total Part A & Part B expenditures ∼$500 billion).

The screening costs do not vary much with nodule size follow-up thresholds. The anticipated cost-benefit would be in the range of $25,000 per life-year saved (2014 dollars), which compares very favorably with mammography and cervical cancer screening and is similar to colorectal screening. From a financial analysis, LDCT screening represents a comparable investment with other validated organ-specific cancer screening activities but since lung cancer is currently so much more lethal than these other cancers, more public health benefit will be potentially realized. (25)

Other Health Policy Aspects of Implementing Lung Cancer Screening

The Patient Protection and Affordable Care Act provided funding not only for evidence-supported cancer screening services but also to start a new national network of patient-centric comparative effectiveness research with cancer screening included as a key interest. (26) This funding was intended to catalyze the evolution of important new clinical management approaches that greatly improve patient outcomes. Dr. Joseph Selby is the director of this new national effort, which is called the Patient Centered Outcomes Research Institute (PCORI). Dr. Selby came to the workshop to explore the intersection between patient-centric outcomes research and this new LDCT approach to finding and curing early lung. The mission of PCORI is to help people make informed health care decisions, and improve health care delivery and outcomes, by producing and promoting high integrity, evidence-based information derived from research guided by patients, caregivers and the

broader health care community. The strategy of PCORI is to frame important research questions as a comparison between two or more options – for screening, diagnosis, or treatment. The trials will consider the range of clinical outcomes relevant to patients conducted in real world populations and real world settings.

An important goal is to evaluate differences in effectiveness and preferences across patient subgroups, which frequently will require a randomized trial design. PCORI intends to focus on important clinical questions but attempts to be sensitive to variable outcomes as a function of clinical or cultural issues. As a result, PCORI has a greater emphasis on understanding personal risk and personal benefit so individuals will be empowered to make better personal health decisions based on solid evidence. Over time, a number of clinical trial methodologies will be used to ask relevant questions but this approach will also use pragmatic trial designs where clinical information available through electronic medical records provides the data to examine the actual study question. Examples of this evolving approach were discussed, especially in regard to the “rapid learning” approaches endorsed by the National Academy of Sciences.(27)

Faced with this challenge of providing high quality, economical and accessible community-based LDCT screening, Laurie Fenton Ambrose, President of the Lung Cancer Alliance (LCA), outlined how this organization is working towards a national solution. Along with a number of institutions that provide LDCT screening services, LCA has assembled a consortium called the National Framework for Excellence in Lung Cancer Screening. The central tenet is that all screening institutions will incorporate evidence-derived national best practices into the components of their screening process. (28) These “Framework” institutions will track and make public their clinical outcomes and they will continue to integrate improved approaches so that the screening process continues to dynamically improve. Another crucial tenet of the “Framework” is recognition of the basic rights of an individual participating in lung cancer screening to have a clear and objective presentation of the potential harms and benefits of LDCT screening. To date over 180 institutions across the United States have joined the consortium and adopted its principles. The Lung Cancer Alliance is committed to ensuring that this mechanism is a conduit back to sites with regard to evolving information about improved screening approaches.

Action Items Relative to Health Policy

Despite remarkable progress with the national implementation of lung cancer screening that is currently proceeding, three health policy priorities emerged as important action items. The first was a proposal to send a letter to CMS asking for full reimbursement coverage of LDCT screening on a national level to ensure equitable access for this new and important cancer screening service. The next was to support the Department of Defense and its Healthy Base Initiative. (29) The final recommendation was to explore commissioning a study by the Institute of Medicine of the National Academy of Sciences on imaging research as it relates to lung and heart disease.

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