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

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2014 EXECUTIVE SUMMARY

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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.

Summary
The Prevent Cancer Foundation has sponsored a lung cancer workshop since 2004, exploring the application of quantitative CT imaging in the management of early lung cancer. Seeds planted over the last decade have blossomed in a particularly favorable fashion. Who could have imagined a decade ago 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? In parallel with this remarkable development, new federal legislation (the Affordable Care Act) would require that every commercial payor implement provisions to deliver cancer screening service recommended by the USPSTF, without co-pay, as a routine service. Does lightning strike twice in the quick succession? Yet at this Prevent Cancer Foundation Workshop, Tobacco-induced Disease: Advances in Policy, Early Detection and Management, we found ourselves on the brink of national implementation of low-dose CT cancer screening.

This was the central message of the overview presented by James Mulshine to launch the workshop. The workshop steering committee's technical experts included David Yankelevitz, one of the founders of quantitative lung cancer imaging; 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 and Laurie Fenton. 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 disease mortality. 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 integration of experts in technical quantitative imaging issues with health policy experts created a challenging but critical conversation.

In this forum, we have been reviewing progress with the application of quantitative imaging not only to early lung cancer detection but also to evaluate early COPD and lung injury. LDCT is emerging as an informative biomarker of cardiovascular risk as well. The goal in this regard is to leverage the full information load acquired in the course of LDCT screening, as well as to improve the dialogue with individuals regarding optimal reduction of tobacco-related disease risk and mortality.

Over the previous ten years, through publications and networking, the Workshop has been successful in advancing the dialogue on how to best integrate quantitative imaging into early lung cancer (Mulshine et al.2013). This year the keynote address, entitled "Bringing Precision Quantitative Imaging to Manage Major Chronic Diseases," was given by Dr. Dan Sullivan. 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 was discussed by Dr. Sullivan as an example of a public-private partnership between investigators and the Institute of Medicine to develop a forum to address relevant issues in an ongoing process. 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 the Radiological Society of North America (RSNA) initiated the Quantitative Imaging Biomarker Alliance (QIBA) to catalyze the process of "industrializing" imaging biomarkers. 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. Currently these efforts involve development of quantitative approaches with a number of imaging modalities.

Spiral CT is one of the key modalities for quantitative development, 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 consider to reduce reader variability and then minimize measurement methods variability.

A major contribution of the QIBA process has been in the area of methodology in the 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 validate a "claim"—or a statement of how reliable the volumetric image measurement is.

A number of research projects have been funded by QIBA to sort out the complex issues with regard to defining the variance of imaging volume measurement and many have included working with phantoms and synthetic digital reference objects to enable objective cross referencing on the volume assessment. The goal of QIBA is to demonstrate actual improved clinical utility 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.

Faced with this new challenge of providing LDCT screening, Laurie Fenton, President of the Lung Cancer Alliance (LCA), outlined how this Foundation 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 (http://www.screenforlungcancer.org/national-framework/). These "Framework" centers 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.

Claudia Henschke of Mt. Sinai discussed an example of how lung cancer screening improvement could evolve using "big data". In a recently published analysis, Henschke used the 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 with > 6mm. (Henschke et al. 2013) The robustness 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. (Yip et al. 2014)

A recent addition to the annual Prevent Cancer Foundation Lung Cancer Workshop is the presentation of the James L. Mulshine, MD, National Leadership Award. This award recognizes leadership in reducing the public health burden of tobacco-related premature death. CVS Caremark was recognized this year for its bold decision, announced in February 2014, to discontinue the sale of tobacco products in their stores by October 1. The award was accepted by Dr. Nancy Gagliano, Chief Medical Officer of the CVS MinuteClinic. Prevent Cancer President and Founder Carolyn Aldigé outlined the rationale for the award in a letter to CVS Caremark's CEO. "We all know cigarette smoking is the most common risk factor for lung cancer, with risk significantly increasing the longer an individual smokes. Educating the public on the dangers of tobacco continues to be a crucial first step in winning the war on cancer. CVS Caremark's courageous decision to remove tobacco products from its stores will help to reduce the incidence of lung cancer and the devastation it creates." Dr. Gagliano noted in her acceptance comments that the entire management team was involved in this decision but it was uniform in its resolve to be a trusted in voice in health care and so that trust could not be realized if they continued to sell tobacco products.

The next series of presentations focused on the shared utility of quantitative CT in providing a window on the presence or progression of early COPD in this heavily smoke-exposed population.

The use of big data is also being explored in the family of pulmonary diseases resulting from tobacco exposure, such as with the consortium funded by the National Heart Lung and Blood Institute COPDGene Project (www.copdgene.org). In his overview Raul San Jose Estépar

commented on the imaging approaches used to quantify disruption in lung structure (parenchyma, airways and vasculature) and function that can be assessed by LDCT (San Jose Estepar, AJRCCM, 2013). He also pointed out how COPD outcomes mirror the severe morbidity and mortality experienced with lung cancer (Zulueta et al, Chest, 2011). He also demonstrated how quantitation of structures such as the pectoralis muscle is a more informative biomarker than BMI for outcomes with pulmonary diseases (McDonald, Annals ATS, 2014); 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 very provocative presentation, Harvey Hecht outlined 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 suggests 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. 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 this process is developed with rigorous evidence. (Hecht in press)

A new opportunity to maximize clinical information from LDCT emerges with the evaluation of breast density as presented by 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. It showed highly favorable results and in addition demonstrated the potential for automated computer-assisted methods to be used as well. She also highlighted the various additional areas where more comprehensive work in this area is still needed and set forth an agenda for further research on CT derived information on the breast (Salvatore et al. 2014).

In the next presentation, the progress with iterative reconstruction was discussed from an industry perspective. Roshni Bhagalia outlined the steps in software development to improve the recovery of critical image signals to best evaluate for potential lung cancer. 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 (Mathieu et al. 2014). However, further research is required to fully understand how this tool can be best applied within the complex setting of lung cancer screening.

Rick Avila presented on two pressing technical issues related to quantitative lung cancer imaging particularly as it relates to lung cancer screening and the management of small nodules. The first area was on the rationale and recommendations for volumetric change percentage thresholds when assessing if a solid lung lesion is increasing or decreasing in size. The 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.

Mr. Avila also presented on recommendations for establishing an image acquisition protocol for simultaneous screening of early lung cancer, coronary artery disease, COPD, and breast cancer. One of the largest 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 recommended 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.

Dr. Tom Baer from Stanford University gave an overview of several fields employing quantitative imaging methods 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: generation of very large data sets, the 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.

The evolution of lung cancer surgery has been remarkable. Nasser Altorki outlined the steps from the routine and extensive resection of an entire side of the lungs to the more tailored endoscopic-mediated limited resection frequently done for a screen-detected lung cancer. As a result of this transition, the reduction in surgical complications has been dramatic. This reduction in post-operative morbidity includes parameters such as lower rates of atrial arrhythmias, lower re-intubation rates, reduced need for blood transfusion, shorter chest tube duration and 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. Natasha Leighl outlined options with pre- or post-operative chemotherapy and preoperative window studies. These approaches involve an array of emerging tools that are being explored in the use of targeted therapy in advanced stage lung cancer, including molecular profiling to align the appropriate drug with the actual tumor biology of a specific patient. Molecular tools can also be used to analyze tumor tissue to determine risk profiles beyond the usual clinical features and examples from clinical trials with advanced disease are already demonstrating the feasibility of such approaches. Other approaches discussed by Dr. Leighl included 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. 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.

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. 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 PMPM (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.

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. This funding was intended to catalyze the evolution of important new clinical management approaches that greatly improve patient outcomes. 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 trial 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 of 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.

Breakout Summaries

The final activity of the meeting was to review the issues prioritized by the two Breakout Groups.

The first report was from the policy breakout group, which focused on three important action items :

- Sending a letter to CMS asking for full coverage of LDCT screening on a national level;
- Engaging the Department of Defense and its Healthy Base Initiative;
- Exploring commissioning a study by National Academy of Sciences on imaging research as it relates to lung and heart disease.

The second report was from the technical group and the focus of that session was on components of registries to monitor quality assurance.

- It was recognized that a model for quality monitoring comes from the American College of Radiology where they have a program to monitor CT scan dose, 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 provides 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 files but to also assess image quality directly using software that can analyze the actual images. In this way, a more comprehensive quality assessment can be provided.
- 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 idea that the development of a large, easy to use quality assurance registry should be developed 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.

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