Use of High-Resolution CT Imaging Data in Lung Cancer Drug Development: Measuring Progress

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Lung cancer is the leading cause of cancer death throughout the United States.[1] Despite massive efforts, tobacco consumption continues to grow, with a large and predictable impact on premature mortality across the globe.[2] There is an urgent need to improve outcomes for lung cancer patients, but the process of developing more effective drugs for lung cancer is hampered by the extraordinary cost of pharmaceutical development and a cumbersome development process. While many factors contribute to high development costs, one of the most significant is the cost of clinical validation trials. This cost is increased by the lack of precision inherent in using the manual measurement technique for drug response evaluation using the current standard approach, called the RECIST criteria (Response Evaluation Criteria in Solid Tumors).[3] RECIST is the validated tool used in most clinical trials.

The Lung Cancer Workshops have focused on developing image-processing tools to be used in evaluating drugs to manage small, early-stage cancers. The use of RECIST has not been validated for use with tumors under 1 cm in diameter. Since management of early cancer will be a progressively greater focus of drug development, defining and validating a new approach to drug response assessment is a critical challenge to progress in treating early lung cancer.

The purpose of the Fifth Prevent Cancer Foundation (PCF) Lung Cancer Workshop was to review progress in the management of drug therapy using image-processing approaches with spiral computed tomography (CT),[4] including consideration of drug response in chronic obstructive lung disease (COPD). This combined focus was based on the frequent comorbidity and clinical overlap between these two tobacco-related diseases, in part, related to shared molecular mechanisms of pathogenesis (Table 1).

The Workshop was held in Oak Brook, Ill, on April 26-27, 2008. It was cosponsored by the PCF and the Optical Society of America (OSA). A major interest of PCF is to encourage development of drug therapies for early lung cancer, and OSA is promoting the innovative use of image-processing tools in clinical management.

**Early Lung Cancer Management**

Dr. James Mulshine of Rush University Medical Center gave an overview of the goals of the Workshop and reviewed past progress and the current lung cancer research environment. Small-volume primary lung cancer is the area where image-processing techniques for quantitative evaluation may have their greatest impact.

Supporting this focus on early lung cancer management, a recent report from Taipei analyzing the results from six prospective CT screening studies using a three-state Markov model with a Bayesian approach suggested that this approach was promising.[5] Evaluating all available published lung cancer screening data that met their a priori criteria and assuming a 10-year time horizon of follow-up, they found that spiral CT had a median sensitivity of 97% and advanced the diagnosis of lung cancer to 1 year earlier than chest x-ray. The authors concluded that with annual CT screening there would be an estimated 23% mortality reduction with a relative risk of 0.77 (95% confidence interval = 0.43–0.98). From a comparative perspective, this preliminary result approached the mortality benefit seen with mature breast cancer screening trial results,[6] highlighting the significant potential in managing early lung cancer.

**Slow Progress in Image Acquisition**

Publications from past Workshops have included an article that reviewed progress up to the fifth meeting[4] and the first OSA monograph, which included in-depth reviews on aspects of quantitative imaging for drug evaluation from previous Workshop participants.[7] A key strategy outlined in the
monograph is to make Digital Imaging and Communications in Medicine (DICOM) image files from research papers available for postpublication evaluation as a research resource, to address the challenge of accumulating sufficient numbers of useful images associated with clinical outcomes data.

This led to a dialogue with Dr. Anna Barker, Deputy Director of the National Cancer Institute, which resulted in the development of the Response Imaging Database for Evaluating Response.[8]

However, in terms of accumulating images for drug-response assessment software, the acquisition of sufficient numbers of paired, characterized high-resolution, thoracic CT image files from individuals before and after receiving cancer drug therapy remains a challenge.

Defining the reasons for the slow progress in acquiring images has been a persistent concern of all the previous Workshops. Issues that have been identified include establishing “ownership” of the images, and Health Insurance Portability and Accountability Act (HIPAA) concerns, institutional review board (IRB) concerns, and other regulatory issues. One surprising aspect of this problem has been the amount of professional time required to acquire, de-identify, distribute, and then verify the image file-sharing. Much of this strategic problem relates to the heterogeneous way patient images are managed across inpatient and outpatient health-care settings. This makes it very difficult to link serially acquired images from an individual patient undergoing cancer therapy with the eventual clinical outcome of that patient.

A strategy was proposed for academic medical centers to more effectively organize their image storage and distribution infrastructure as an integrated enterprise resource. The goal would be to have the imaging data systematically stored in relationship to other clinical data provided by electronic medical record. If the clinical and imaging information systems are aligned, this may allow for rapid and efficient acquisition of imaging and related translational research data at incremental cost, so that validated clinical outcomes data will accurately define evolving “ground truth.”
Table 1

Specific Topics Discussed at the Workshop

- Progress in the evolving capabilities of helical CT imaging, image processing in major tobacco-related diseases of the thorax
- Regulatory implications of using changes in volume or other quantitative measures as a metric for clinical drug response
- Procedures to perform cross-platform comparisons of changes in imaging results when evaluating longitudinally acquired scans from the same individual on equipment manufactured by different companies
- Measures to exploit image processing as a core tool for rapid and robust clinical trials, particularly using reference tools to start benchmarking performance of new algorithms to evaluate significant clinical metrics
- Progress in developing image/clinical outcomes archives to facilitate the development and validation of image processing and related tools to measure drug responses from high-resolution CT scans
- Definition of concrete next steps to advance the field, building momentum from previous meetings

CT = computed tomography.

This approach is general strategy for all types of imaging tools, including magnetic resonance
imaging and positron-emission tomography. The gap in the availability of images linked to clinical follow-up is an important, underrecognized challenge for improving imaging research, especially in early disease management. Imaging research is generally perceived to be a radiological problem, but this strategic gap cannot be overcome unless radiologists work closely with clinicians to allow images to be routinely linked to clinical outcomes in large numbers of patients.

**Imaging Issues in Lung Cancer**

The specific application of imaging in lung cancer management is limited by significant unmet needs. Series of cases are required for imaging tool validation in each clinical management setting, and in these different settings, there are distinct challenges for image analysis.

Tumor-node-metastasis (TNM) staging has been the cornerstone of defining patient prognosis and also provides a useful framework for discussing the nature of the distinctive image-processing challenges across the spectrum of lung cancer. For clinical trials in stage IV lung cancer, imaging is typically concerned with characterizing the sites of metastatic disease (M+ disease). In this setting, since the disease can extend throughout the body, volumetric CT of the primary lung cancer is often not the pivotal basis for determining drug response. In this circumstance, disease progression is commonly at a known site of metastatic disease or with detection of a new site of metastatic involvement.

In the setting of stage II/III lung cancer, there is typically involvement of regional nodal sites with cancer (N+ disease). This is also a challenging setting since the involvement of mediastinal nodal structures can be complex and bulky. In addition, since the mediastinum is the confluence of so many vascular, lymphatic, and bony structures, reliably segregating the volume involved with nodal cancer can be quite challenging. For this reason, image-processing strategies involving only volumetrics may have limited utility.

In the setting of stage I lung cancer, the standard approach is to use surgical resection. Recently, a new trial structure has been employed to evaluate the effect of brief exposure of new drugs on stage I lung cancer patients, while they are awaiting surgery. This experimental trial structure is called a neoadjuvant window-of-opportunity trial (referring to the 2- to 3-week time interval during which a patient is awaiting thoracic surgery to remove his or her cancer). In this trial design, the primary endpoint is determining volume changes in the primary lung cancer. This measurement can be quite accurate, as the boundary of the tumor is surrounded by air-filled alveolar tissue allowing for an exquisite signal-to-noise ratio.

This trial design also provides a rare opportunity to derive information about the drug response to untreated clinical lung cancer. Typical lung cancer drugs are initially evaluated for disease activity in the setting of clinical cohorts that have already failed one or more types of chemotherapy. Drug candidates must be used for many years in heavily pretreated patients before these agents will ever be evaluated in the setting of early lung cancer. Developing a strategy to accelerate this process is critically important and complements new strategies for drug development proposed by the US Food and Drug Administration (FDA).[9]

The window-of-opportunity trial design also allows for direct comparison of analogs for targeted drug development using efficient, new randomized design strategies.[10] Finally, window trials could also be used to define optimal drug dosing for a new agent by virtue of the serial tumor tissue sampling protocols built into this type of study. Molecular analysis sampling tumor tissue before and after drug exposure can be used to determine if known downstream molecular signaling is blocked as expected by the doses of drug used in the trial.

**Window-of-Opportunity Trial**

An important accomplishment of this Workshop series was the reported completion of a neoadjuvant window-of-opportunity trial by Dr. Nasser Altorki of Cornell University Medical Center. Dr. Altorki outlined the rationale for this new clinical trial approach in evaluating new targeted therapeutics in untreated, primary lung cancer and discussed the completion of a multicenter, neoadjuvant, window-of-opportunity trial performed in collaboration with GlaxoSmithKline. This trial evaluated the effect of a dual-kinase, vascular endothelial growth factor inhibitor (pazopanib) on tumor volume as measured by high-resolution spiral CT images performed before and after a brief preoperative course of the orally administered agent. In this trial, the drug was well tolerated and did not interfere with curative surgical management.

Workshop participants suggested that the systematic molecular analysis of preoperative biopsies and resected tumor tissue will define what drug targets are present in which types of tumors and how often. The molecular analysis done in parallel with the imaging should establish which downstream signaling pathways are affected by the drug exposure and suggest logical targets for subsequent combination drug therapy.
Shortly after the Workshop, Dr. Altorki presented the neoadjuvant trial results with pazopanib at the American Society of Clinical Oncology (ASCO) annual meeting.[11] In this 26-patient evaluation, evidence of tumor volume reduction was seen on spiral CT of the chest in 82% of the patients receiving a 2- to 3-week course of pazopanib. Only modest drug side effects were reported in this trial. The preliminary results of the biologic monitoring of tumor response from the specimens obtained in the course of this study paralleled the pattern of response seen on the imaging endpoints of the trial.

Areas of Progress in Thoracic Image-Processing and Validation Ricardo Avila, of Kitware, Inc, gave an overview of lung cancer and COPD image analysis methods and discussed progress in image-processing over the past year. This overview included a proposal for a minimum recommendation of CT acquisition parameters for future lung cancer clinical trials. He also discussed the development of an infrastructure to support an open database of patient-donated CT scans. The patient advocacy group, Lung Cancer Alliance, had completed a pilot project named “Give-A-Scan” with a small group of patients. In this project, patients donate their own CT scan data and provide basic clinical outcome data. The project received 6.2 GB of CT scan data from 15 donors, including 10 cases of lung cancer. The pilot project will be followed up with a larger project over the next year. Mr. Avila next discussed a recommendation from last year’s Workshop to create an open source set of reference methods for measuring tumor size. He announced that a consortium of federal and OSA funding had been committed to support the development of an open source lesion-sizing tool. Another recommendation from last year’s Workshop was to establish a method to measure the progress of investigators working on CT lesion-sizing methods. In response, the National Institute of Standards and Technology (NIST) developed an algorithm validation matrix called BioChange 2008 at the Workshop. To address the final recommendation of last year’s Workshop, Kitware developed a mailing list and wiki for constant communication throughout the year. This has been a functional resource for the past 10 months.

Dr. Charles Fenimore of NIST announced the BioChange 2008 project and described efforts to precisely measure the performance of software methods that quantify the size of lesions in CT scans. Dr. Fenimore provided the goals and rationale for the project and summarized early results associated with the acceptance of benchmarking data from a number of institutions. Subsequently, Dr. Lutz Guendel of Siemens, Dr. Michael Lee of Phillips, and Dr. Anthony Reeves of Cornell University provided additional results and feedback. Each presenter reviewed the challenges in evaluating lesion-sizing performance, and all reported on the critical need for a larger collection of phantom and clinical images.

In the next session, Dr. John Childs and Mr. Avila reviewed the significant progress that they have made jointly in developing infrastructure to support open publication of imaging research, including the publication and review of large collections of CT data. Dr. Charles Clark from the physics group at NIST presented new approaches to image evaluation standardization and outlined NIST plans and opportunities.

Next, Dr. Brian Duchinsky of GE Healthcare, Dr. Lee, and Dr. Guendel discussed the future of CT-imaging progress. The presentations all suggested a bright future for sustained imaging progress based on enhanced resolution, faster image-processing times, and tighter integration of image-analysis capabilities into workflows. This session ended with a panel discussion that outlined the importance of developing better image archival resources to ensure the optimal clinical integration of the future generation of CT scanners.

Dr. Joseph Reinhardt of University of Iowa discussed progress with image processing in COPD. This is an area of rapid progress, and while there were some similarities in analysis approach, he also outlined a very powerful approach to measuring deformations of the lung between inspiration and expiration. This approach has the potential for identifying and quantifying compromised areas of the lung parenchyma and may help support a range of lesion-sizing and analysis methods in the future. A panel of accomplished imaging scientists then reviewed the topic: How to collaborate to accelerate response assessment for lung cancer. Panelists included Dr. Fenimore, Mr. Avila, Dr. Terry Yoo of NIH, Dr. Reeves, and Dr. Thomas Baer of the OSA. Dr. Yoo provided a presentation on the importance of open science—the movement dedicated to sharing of scientific data and collaboration within a global community of researchers—and urged the lung cancer research community to adopt open publication of datasets and algorithms. The group was uniform in endorsing the importance of open publication and aggregation of published imaging files and associated meta-data as a foundation for success in this new field.

Molecularly Targeted Drug Therapy and Regional Drug Delivery Dr. Phil Bonomi of Rush University Medical Center presented an overview on the current state of progress with lung cancer drug
development. His presentation outlined the mechanistic targets for the major ongoing clinical trials in lung cancer. Dr. Bonomi’s presentation emphasized the need for new drug options for advanced-staged disease but echoed the sentiment that the greatest hope for major breakthroughs exists for strategies associated with treating early cancer.

Dr. John Patton of Nektar Therapeutics reviewed recent progress in approaches to regional lung delivery as a strategy for more efficient drug therapy for early disease. Dr. Patton used his extensive experience with the development of aerosolized insulin as a model of the aerosolized drug development process. Lung cancer arises from the chronic deposition of tobacco combustion products in the airway through the aerosolized delivery of carcinogens. Having efficient pulmonary drug delivery capability to deposit targeted therapeutics to the same cells that have been transformed by tobacco smoke is a conceptually attractive tool to explore for early lung cancer management.

In a related presentation, Dr. Jack Lee of the University of Texas M.D. Anderson Cancer Center presented a new and potentially more efficient trial design for the evaluation of new targeted therapeutics. Dr. Lee outlined how patients can be allocated to different randomized arms of a clinical trial using information derived from evaluation of the baseline biopsy to the tumor biology specific to each patient. This biologic information can be used to predict potential patient response and increase the probability of a favorable clinical response to the drug therapy. This adaptive Bayesian design has the potential to maximize the efficient use of volunteer participants and improve overall drug response.[12]

The status of cardiac imaging was presented by Dr. Stanley Clark of Midwest Heart Center. This topic reflects the shared tobacco-related pathogenesis of lung cancer and COPD with coronary artery disease.

In the final set of presentations, Dr. Reeves reviewed preliminary results of a comparison of approaches to determining lung nodule volume and showed an interesting array of cases that exemplify the types of challenges anticipated in this field. Dr. Nick Petrick of the FDA presented on the assessment of nodule volume error and presented preliminary results obtained with his group’s anthropomorphic phantom.[13] Finally, Dr. Fenimore outlined initial results comparing software algorithms for lung cancer and discussed plans for NIST to develop additional capabilities to facilitate quantitative imaging processes.

**Imaging Technology Group Report**

Leading off the subsequent reports by the breakout groups, the imaging technology group focused on the evaluation of NIST’s Biochange 2008 Lung Cancer Assessment Metric. A point of agreement among the participants was the need for a greater number of cases with high-resolution images associated with reliable markup of lesion boundaries. The next concern was whether a group of radiologists or a new software tool should be considered as the gold standard for defining the lesion boundary. The group agreed that this was a dynamic issue for the foreseeable future. They also noted the need for a greater number of cases in which treatment response and other clinical outcome information is available. This triggered a complex discussion on how to define “ground truth” in regard to clinical outcomes—another topic for which the answer was heavily dependent on the specific trial context.

The imaging technology breakout group established three main recommendations. First, they agreed that continued evaluation of therapy assessment algorithms was important to sustaining progress in the field. The second recommendation focused on ensuring that open databases containing an abundance of thin-slice CT scans of lung cancers are assembled for algorithm development and evaluation. Finally, they emphasized the importance of obtaining fundamental acquisition characteristics for the assembled CT scans, such as the three-dimensional point spread function and noise properties. The deployment and use of the pocket calibration phantom developed by Cornell and NIST as well as the concept of embedding calibration phantoms into CT-scanning tables were discussed as potential solutions.

A number of speakers commented on the common lung imaging challenges shared by lung cancer and COPD. These tobacco-induced diseases share anatomy and disease pathogenesis, and COPD often arises in individuals afflicted with lung cancer. A research opportunity in this regard may be the reciprocal contribution of image processing across the drug development efforts for these two diseases and perhaps into cardiovascular disease. The challenge is to create support for this approach across academia, government, the advocacy community, and industry, to allow the critical cross-disciplinary conversations to proceed while redundant efforts are minimized and critical mass of stakeholders is ensured.

The clinical research breakout group discussed many technical issues surrounding optimization of
imaging-driven trials. However, their key message was the essential need for effective cross-disciplinary teams. Accrual of patients to these studies occurred most readily in centers that had ongoing early-detection research efforts, where early-stage cancer patients were being routinely identified for surgical intervention. Close coordination of radiologists and the diagnostic workup team was critical to allowing the protocol proceed smoothly. Many trial design issues, especially in regard to optimal metrics (volume change, change analysis, or a variety of other endpoints) were discussed, with no clear winner evident at this early time. The approach suggested by Dr. Lee, using the Bayesian adaptive design, was deemed attractive for efficiently evaluating drug candidates in early lung cancer.

The most pressing challenge identified by the strategic breakout group was the perception that the potential of imaging tools in drug development is largely unrecognized by most clinicians, many in industry, and most importantly, the public. There is a need to disseminate information to potential stakeholders about the near-term benefits in a setting where modest research investments could have a great impact.

**Conclusions**

The meeting concluded with an appreciation of the contribution by NIST in making concrete steps to start the algorithm-development process. The completion and reporting of the first neoadjuvant, window-of-opportunity trial emerging from this Workshop series was the high point of the meeting. Participants recognized the great progress made with image processing in both the COPD and cardiovascular imaging communities, and the group was excited about greater interaction between investigators from these related areas of imaging research. Workshop attendees expressed continued frustration about the slow accrual of imaging cases, especially at high resolution. The Lung Cancer Alliance’s Give-A-Scan project and the Prevent Cancer Archive developed at Cornell were both appreciated as important efforts. Extending the window trial strategy to additional molecular targets is a key opportunity in efforts to improve the lung cancer drug development process.

**References:**

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