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New Imaging Approaches for Understanding Lung Cancer Response to Treatment

J de Ryk¹, E Namati¹, J Thiesse¹, and G McLennan¹

¹Department of Internal Medicine, University of Iowa, Iowa City, Iowa, USA

Abstract

The survival rate for lung cancer patients has barely improved over the past 30 years. New evaluation benchmarks for cancer response are needed to test therapy agents in a cost-effective and timely manner. From recent work, it is evident that primary lung cancers are very complex structures containing not only cancerous cells but also fibrotic and inflammatory cells and necrotic tissue. A greater understanding of the three-dimensional structure of primary lung cancer is emerging, allowing for the first time an appreciation of how this biomass is represented in medical imaging data. It is only through a greater understanding of the lung cancer biomass that we can define rational and early-response measures, including specific cellular responses such as cancer cell death or growth inhibition. In doing so, we can define response metrics that will shorten new drug discovery times and reduce costs, allowing for the evaluation of many more agents with therapeutic potential.

Recent developments in imaging technologies, especially multi-row detector computed tomography (MDCT), have resulted in the early detection of lung nodules. However, of these early detected nodules, only a very small proportion is lung cancer. Early diagnosis, at a time coincident with detection, is not currently possible, and the current recommendations are for MDCT observation over many months to assess potential nodule growth, with the notion that nodule growth is a reasonable surrogate for the cancerous phenotype.¹ This delay between detection and diagnosis is referred to as the lung cancer paradox.² Significant efforts are under way to improve the diagnostic methods for lung nodules using advanced MDCT applications, including virtual bronchoscopic directed pathway finding and electromagnetic supported navigation and guidance strategies, together with ultrathin optical bronchoscopes that are informative for color, optical coherence tomography, confocal microscopy, fluorescence, and spectroscopic applications. Meanwhile, the survival rates for lung cancer remain static at 15%, whereas those for many other forms of cancer continue to improve.

New therapeutic pharmaceutical agents are urgently required to treat lung cancer, one of the most aggressive tumor types, with metastases to draining lymph nodes as well as the

bloodstream. Many of the newer pharmaceutical agents primarily work not by eradicating cancer cells themselves but by affecting the cancer cell microenvironment, such as the vascular system. There are many new agents in development for lung cancer therapy; however, therapeutic end points are still restricted to either patient survival or some very obvious reduction in cancer size, usually in a two-dimensional measure using the Response Evaluation Criteria in Solid Tumors. If patient survival is taken as the standard, then studies will be extremely expensive and require a long time; in addition, there are only enough patients to evaluate a small proportion of the available new agents and agent combinations. If only gross measures of cancer size are taken into account, response may not be evaluable for several months, and agents that work to prevent cancer growth rather than reduce cancer cell numbers are not evaluable at all. Other articles in this journal evaluate new methods for more rigorous assessment of lung cancer size to help with cancer-specific response evaluation. These currently accepted methods for lung cancer therapy outcomes are clearly not serving the patient population well, and newer knowledge—as well as newer thinking in the assessment of response in the cancer patient—is required. We propose a third level of response assessment based on the pharmaceutical agent's mechanism of action. Within a patient's targeted lung cancer it should be possible within a short period to assess the response of individual cells to the therapy in question, using a combination of the optical imaging strategies mentioned above. For instance, if cancer cell death is expected, or if a cell receptor is occupied by a specific agent, these events should be measurable through optical methods, and perhaps also by specific external imaging modalities that are currently in development. This third level of therapeutic response would greatly facilitate the drug evaluation pipeline by allowing many more agents to be screened in human populations in a rigorous scientific and affordable manner.

We have outlined here the two major problems that currently exist in the treatment of lung cancer: the difficulties in diagnosis based on detection of small lesions and the inability to rapidly assess therapeutic effect. Significant efforts are under way to solve both of these problems. Most of the potential solutions are exploring the significant recent advances in three-dimensional (3D) imaging hardware and software using MDCT and optical devices or their combination.³ However, because we currently know almost nothing about the 3D structure of the lung cancer biomass, we are unable to exploit these advances, and an understanding of this structure is absolutely essential for the field to advance.

A PROCESS MODEL FOR UNDERSTANDING LUNG CANCER BIOMASS STRUCTURE

It is vital for the continued maturation of lung cancer diagnosis, treatment, and treatment evaluation approaches that a 3D-understanding of the structural content of lung nodules be obtained. We have developed a process model for the acquisition and registration of multimodal data sets of lung cancer nodules that permits the exploration of nodule volume content and cross-modality representation.

Following preoperative MDCT imaging, human lung nodules are obtained from consenting patients requiring surgical lobectomy. Following specific lobar fixation, the isolated nodules are imaged using MDCT, computed microtomography, a custom-designed 3D serial

microscopy system—the large image microscope array system (LIMA)—and histopathology. The unique LIMA data set serves as the basis for the rigid and nonrigid registrations required to accurately align the radiological and histological data. A surgical pathologist with expertise in pulmonary pathology manually traces regions of each tissue type in the digitized histopathology data, producing detailed 3D maps of the tumor biomass that are related, voxel to voxel, to the radiological data sets. It is then possible to create 3D reconstructions of the nodule content.

Most non-small cell lung cancer nodules are histologically heterogeneous, a factor not appreciated by many investigators and one that is also very poorly documented and studied. The nodules typically consist of necrotic tumor cells, fibroblastic stromal tissue, and inflammation, with malignant cancer cells comprising only a small percentage of the nodule volume.

The lung nodule biomass vasculature can also be studied within the process model. This can be achieved via the acquisition of presurgical perfusion MDCT data, together with the administration of indocyanine green systemically to the patient at the time of surgery. Commonly used in human studies, indocyanine green is a fluorescent agent that binds to human serum albumin and remains within the intravasculature compartment. The vasculature in the LIMA and histology data sets will therefore retain the fluorescent signal. This 3D vasculature information would be of significant use in understanding the proportion of blood flow to each tissue type in the nodule, impacting drug delivery. In addition, with targeted optical imaging within the lung nodule biomass prior to resection, the indocyanine green distribution can also be visualized *in vivo*.

It is important to note that this process model, summarized in Figure 1, was not designed to be incorporated into clinical therapeutic trials, although it may be adapted for that purpose. The model was initially developed to establish a database from which ground-truth knowledge and understanding can be gained.

EARLY RESULTS FROM THE PROCESS MODEL

The developed process model overcomes some major challenges, for example, effective tissue fixation that preserves the inflated structure of the surrounding alveoli as well as the radiodensity of the tissue and the establishment of the LIMA data set, which reliably links the spatial information of the nondestructive CT data sets to the corresponding histology.⁴ The registration of these multimodal, multiresolution data sets is also complex.

High-resolution MDCT data sets that contain a higher level of structural information than clinical MDCT protocols are being acquired. These will allow for more accurate registration of MDCT information to the *ex vivo* MDCT, computed microtomography, LIMA, and histology data sets. We expect to be able to explain the MDCT gray-level heterogeneity of lung nodules in relation to the histological findings. Additional perfusion information will also permit the incorporation of blood-flow information into the data set.

Early results from the process model indicate that the composition of adenocarcinoma lung nodules is very complex. In these preliminary cases we have found that the maximum

component of malignant tumor cells in lung nodules is 55%. That is, for most lung nodules, our findings have indicated that the malignant tumor component comprises approximately half of the nodule biomass. This will be examined further with the addition of more cases to the study.

RESPONSE TO TREATMENT: HOW TO EVALUATE EFFECTIVE RESPONSE?

Informative methods for the evaluation of lung cancer response to treatment are required. Not only is this a requirement for separating effective from ineffective treatment approaches, but in addition, a standardized approach is required to allow accurate comparison of results across studies so that the true efficacy of alternative drugs can be cross-correlated.

The longest-standing measure of treatment response has been survival time of treated patients compared with untreated control patients. More recently, end points such as progression-free survival or time to progression have been reported. Evaluations of this type are typically conducted on patients with advanced disease for whom traditional treatment approaches have been exhausted. These patients are not ideal subjects for the study of drug development, as it is desirable to develop approaches for treating less advanced disease. To investigate less advanced disease response to treatment, more rapid methods of evaluation are required, which will have several other clear benefits, including shorter pharmaceutical development cycle time and hence lower cost.

The widespread introduction of MDCT scanning into large and small medical centers has resulted in a means by which response to treatment can potentially be measured over shorter time periods. Efforts have been made to standardize the evaluation of nodule response to treatment using this modality. The Response Evaluation Criteria in Solid Tumors was introduced in 2000 as a set of rules connecting changes in nodule-longest-diameter measurements with four response categories: complete response, partial response, stable disease, and progressive disease.⁵ However, this method has recently come under scrutiny because of its inapplicability to cytostatic drugs (which inhibit cell growth rather than kill cells) and its dependence on a single measurement that does not make effective use of the information provided by modern MDCT technologies.⁶ There are other evaluation metrics that aim to improve on the correlation between response and survival, such as the Southwest Oncology Group's lung cancer disease control rate, which includes static nodule measurements as a response.⁷ Also, the Choi computed tomography response criteria incorporate contrast-enhanced tumor density as a measure of response in gastrointestinal stromal tumors.⁸ Nodule size determination based on volume change has also been the subject of recent multi-institutional efforts, including the Lung Image Database Consortium and the Reference Image Database to Evaluate Response to drug therapy in lung cancer.

All proposed MDCT-based criteria for the evaluation of treatment response rely on measurements of tumor size, which brings forth the issue of how to generate reliable, repeatable, comprehensive, and observer-independent measurements. In addition, as indicated above, it is understood through histological evaluation that lung nodules contain a complex heterogeneity of tissue types of which cancer is not the majority, indicating that it

is possible for a treatment to be successful in killing all cancer cells even if it results in a minimal reduction in overall nodule size. Heterogeneity in the gray level of MDCT representation of lung nodules is also commonly observed, and yet the cause of this gray-level variability is poorly understood. An example of the gray-level heterogeneity in both a solid nodule and the more obvious case of a nodule with both solid and nonsolid regions is shown in Figure 2. If lung tumor density values were to be incorporated into an evaluation such as the Choi response criteria, it is important to understand what correlation—if any—exists between regions of cancerous tissue and gray-level heterogeneity.

In addition to using MDCT for patient evaluation, an escalating development in advanced bronchoscopic evaluation techniques is to use, for example, optical coherence tomography or confocal systems for the early evaluation of suspicious lung nodules. This push in technology is aimed at bridging the gap between the identification of a nodule and achieving a diagnosis so that an immediate and effective treatment plan may be developed. However, with advancement in this area comes an increasing need to better understand the variability in lung cancer biomass tissue content and distribution as well as for development of meaningful sampling area standards. As described above, in most cases the malignant portion of a nodule makes up about one-half of the nodule mass, with the remaining solid portion being composed of necrosis, fibrosis, and inflammatory cells. This is of particular importance to bronchoscopic evaluation techniques, which have a limited sampling field. Standards regarding the number of sampling fields required to reliably ascertain the absence of malignant tumor cells must be developed.

We have developed a system that relates, pixel by pixel, large-scale 3D histopathology to the corresponding MDCT scan. The resulting data set can be used to help determine how the true lung nodule boundary, as defined on a cellular level, is represented in other imaging modalities such as MDCT. The resulting gold standard data set for lung nodule boundary can be used to train manual tracers in order to minimize intraobserver variance or to develop accurate automated boundary-detection algorithms. In addition, a greater understanding of the true correspondence between gray-level heterogeneity and lung nodule content can be established. This system can also be expanded to include magnetic resonance imaging and positron emission tomography data sets (Figure 3).

MICRO-OPTICAL IMAGING STRATEGIES

The use of novel micro-optical techniques has recently generated great interest in the pulmonary field for their potential to translate into clinical *in vivo* biopsy systems.^{9,10} Promising techniques include optical coherence tomography,^{11–14} fiber optic spectroscopy,^{15,16} and catheter-based confocal microscopy (CBCM).^{17–22} CBCM systems have been a focus of our group for characterization of normal and diseased lung tissue in mouse models^{23–26} with some early investigation on pig²⁷ and human lungs.²⁸ These systems possess a high sensitivity and specificity because they have the ability to noninvasively resolve cellular structures down to the micron level using reflectance and fluorescence modes. The CBCM system developed in our group was designed to fit the auxiliary channel of a standard or ultrathin bronchoscope and can therefore be used to investigate lung tissue from the airway epithelium down to the alveoli via the subtending

airways.^{23–26,28} Highly sensitive biomarker tagging strategies can be deployed, taking advantage of the fluorescence approach, in which the light of one wavelength is used to excite a specimen emitting light at a higher wavelength.

Using CBCM, we envision at least two distinct optical biopsy strategies: one that uses specific fluorescent biomarker tagging of important cellular structures and therapeutic compounds and a second that assesses general information regarding the tumor microenvironment.

The first strategy for noninvasive tracking of tumor stasis and therapeutic response would be applied in the clinic via unique fluorescent tagging of therapeutic compounds and targeting of receptors/cells using dynamic fluorescent biomarkers that emit different wavelengths of light depending on their functional state, e.g., yellow for normal and red for apoptosis. It is envisioned that the application of the fluorescent biomarkers and therapeutic compounds would be performed sequentially at the site of the lesion through the auxiliary channel of a bronchoscope. Once applied, the CBCM system would begin to acquire cellular images of the interaction between the therapeutic compound and the cancer cells. This approach would allow direct visualization of therapy and target interactions at a cellular level with very high temporal resolution. Also, because this form of assessment would not remove the tissue of interest, problems associated with tissue biopsy would be eliminated.

The second strategy is anchored on the fact that the microenvironment of a tumor is significantly different from its surrounding “normal” tissue and is directly related to its progression. Identification and measurement of such properties as oxygen, glucose, pH, CO₂, temperature, and specific amino acids would be highly useful for such assessment. In this case, absolute values for each property normalized across a population may not be necessary; instead, a relative measurement between “normal” and “suspicious” regions within the same patient may be sufficient.

An example of the CBCM imaging approach on a mouse model of lung cancer (urethane induced) is shown in Figure 4. Here, two regions have been imaged in a living mouse lung: (i) suspicious alveolar parenchyma and (ii) heterogeneous tumor region. In this example, sodium fluorescein has been systemically administered for visualization of general tissue structure, and acridine orange has been applied topically over the region of interest for identification of nuclei.

In the future, the combination of macro-optical imaging techniques such as white light and autofluorescent^{29–32} and fluorescein bronchoscopy^{3,33,34} will be used for the initial identification of suspicious regions, whereas micro-optical techniques such as the CBCM system will analyze and classify the regions of interest, enabling live pathologic assessment. By understanding the complex 3D structure of the lung cancer biomass, the appropriate number of sample points for micro-optical biopsies can be statistically determined. In addition, by understanding the meaning of macro level imaging results, such as gray-level heterogeneity in MDCT or metabolic activity for positron emission tomography studies, this optical sampling of the tumor can be specifically directed to regions of interest.

CONCLUSION

It is clear that the lung cancer biomass remains poorly understood in terms of structure as well as function. Emerging technologies through MDCT, optical imaging, and their synergistic combination are being developed, refined, standardized, and implemented in the clinical setting to advance understanding of the lung cancer biomass. This will significantly impact the diagnosis and the rapid assessment of response to therapy of any detected potential lung cancer. To fully integrate these new methods into this clinical information decision tree, correlation to the pathology within the biomass is fundamental—and for the first time is now also achievable.

The combination of new methods and the associated new knowledge outlined in this article will have a significant impact on new drug discovery, important for altering lung cancer outcomes. Changes in the requirements for the assessment of drug effects are also needed at the regulatory level to fully capitalize on these developments. The personalization of health-care delivery based on imaging modalities in lung cancer is certainly technically within reach and will be a welcome addition to further discovery in lung cancer.

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Figure 1.

Process model for the establishment of a ground-truth database illustrating the imaging approach at each stage of tissue processing as well as the registration techniques applied to align each data set to a common coordinate system such that the multimodal, multiresolution data sets could be compared on a voxel-to-voxel level. LIMA, large image microscope array system; MDCT, multi-row detector computed tomography; micro-CT, computed microtomography.

Figure 2.

Two presurgical multi-row detector computed tomography (MDCT) data sets. The figure shows (a) the heterogeneity within a solid adenocarcinoma nodule and (b) an adenocarcinoma nodule with both solid and nonsolid components. Not only is there heterogeneity in the gray level of the MDCT slices from the nodule with the nonsolid component (b1, b2, and b3), but there is also gray-level heterogeneity in the solid nodule (a1, a2, and a3).

Figure 3.

An example non-small cell adenocarcinoma nodule data set. Shown is a single two-dimensional slice through the data (left) and the three-dimensional representation (right). The data set includes (a) the multi-row detector computed tomography (MDCT) scan of the *in vivo* lung nodule, (b) the MDCT of the fixed, resected lung lobe, (c) the MDCT of the isolated lung nodule, (d) the computed microtomography scan of the isolated nodule, (e) the large image microscope array data, (f) the H&E-stained histology sections, and (g) the pathologist-traced tissue-type maps. These image sets reflect the resulting comprehensive

multimodal cross-registered data set containing density, structure, color, and cellular information relating to the nodule content.

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Figure 4. Catheter-based confocal microscopy imaging of a living mouse lung in which urethane-induced lung cancer has developed. **(a)** A suspicious alveolar parenchyma region. **(b)** A heterogeneous tumor region.