Improving Outcomes for Patients with Lung Cancer

Personalized Oncology at the University of Michigan

Introduction

Each year in the United States, approximately 200,000 people are diagnosed with lung cancer, a disease that takes more lives than breast, prostate and colon cancers combined. About 85 to 90 percent of lung cancers are related to smoking, with half of these cases occurring in former smokers. Nationwide efforts to raise awareness about the risks associated with tobacco use have helped decrease smoking rates in many regions of the country, and as a result, the incidence of lung cancer has started to decline; but there remain a large number of active and former smokers who are at high risk of developing lung cancer.

Despite reductions in the rates of smoking, lung cancer mortality continues to be extremely high, with a less than 25 percent five-year survival for all patients diagnosed with lung cancer. One of the key reasons that lung cancer is so deadly is that it usually does not cause many symptoms, and thus is not detected until it has advanced beyond the early stages.

In addition, while most lung cancers share the exact same risk factors, little is known about why people develop the different kinds of lung cancers. Approximately 85 percent of patients will have non-small cell lung cancers (comprised of adenocarcinomas, squamous cell cancers, and large cell cancers), which often present in the peripheral lung, and if caught early can be treated with surgery alone. A smaller percentage (roughly 15 percent) of patients present with small-cell lung cancers (aka, “oat cell”), which usually present in the central part of the chest; these cancers are treated with chemotherapy and radiation first since they often show responsiveness to these treatments.

Despite a growing body of literature, scientists do not yet understand, at a molecular level, all of the alterations that are associated with the main forms of lung cancer. As a result, there is little variation in the way lung cancers are treated, particularly among non-small-cell cancers. Without more specific information about how and why a particular tumor type develops, patients are left with generic treatment options that are only marginally effective.

U-M Research Offers New Hope for Patients

The lung cancer team at U-M is dedicated to improving this situation for lung cancer patients by developing new strategies to detect and treat lung cancer more effectively. We’re working to uncover the unique and complex nature of every patient’s lung cancer by studying, at the molecular level, the specific genetic alterations present and the biological events that contribute to variations in the malignant behavior. Specific molecular alterations present in the tumors can also be detected in the patient’s blood potentially providing new approaches for early detection of lung cancer.

Ultimately, the purpose of this work is to create a genetic profile of each patient’s lung cancer, which identifies the specific gene alterations and mutations that may have started the disease, and the specific genes expressed in aggressive cancers. Doing so, will enable clinicians to determine where, when, and how to precisely diagnose and then attack the disease with targeted therapies. This revolutionary new approach to cancer care is called “personalized oncology.”

U-M's team of lung cancer experts has undertaken an ambitious lung cancer research initiative to understand the genetic drivers of each kind of lung cancer; develop targeted drugs to attack the disease precisely, at the molecular level; and bring the vision of personalized oncology to fruition within the next decade.

Uncovering the Root Causes of Lung Cancer

Understanding the genetic underpinnings of each instance of cancer is now possible because of major advancements in genetic sequencing technology. The first human genome sequencing project (determining the complete DNA sequence of an organism's genes), led by former U-M professor and current director of the NIH Dr. Francis Collins, was a massive undertaking, ultimately taking two years to complete with a total price tag of nearly $2 billion. Just ten years later, gene sequencing takes only two weeks and costs just $5,000. Within five years, experts expect that sequencing will take only a few days and cost less than $1,000, making it realistically possible to sequence the genome of every tumor in every patient.

U-M scientists have led the field in the use of genetic sequencing for cancer diagnostics. The discovery of genes linked directly to various types of cancer, and the molecular pathways these genes use, has allowed scientists to draw a more accurate road map of the nuances of cancer and its progression. Now, this map is being used to develop therapies that tackle cancer with far more precision. As this important work progresses, oncologists will be able to prescribe therapies specifically designed to attack the underlying genetic causes of each patient's cancer, improving outcomes and leaving healthy cells unharmed in the process.

Our scientists are currently undertaking a pilot study, sequencing the tumors of 100 prostate, breast and blood cancer patients. Lung cancer tumors will be included in the next phase of this groundbreaking research. Our lung cancer researchers have already evaluated hundreds of lung cancers from patients, looking at their genetic changes in the laboratory. The genetic sequencing work will build on these findings and, scientists suspect, will uncover significant molecular variation among patients with the exact same tumor type.

In addition, U-M's lung cancer team is currently establishing lung cancer "xenograft" models, where human tumors are directly implanted into mice and allowed to grow, creating an invaluable laboratory tool for studying human tumors. While genetic sequencing can identify the underlying genes involved in lung cancer, the xenograft models will allow our scientists to study how new treatments affect tumors in live animals. The model will also provide a mechanism for scientists to study how each type of lung cancer develops, identify genetic mutations and other molecular processes to target with drugs, and test new treatments in the lab before ever testing them in humans.

Improving Early Detection

Improving methods to detect lung cancer early is critical to improving the rates patient survival. Recent studies have shown that the use of computerized tomography (CT) scans can improve survival by detecting early stage disease. Unfortunately, CT scans are not precise enough to differentiate between cancerous and non-cancerous nodules. As a result, CT scans detect a large number of benign nodules that, once found, require regular evaluation or surgeries to prove that they are not cancer – the result is

a large number of unnecessary operations or follow up scans. CT scans themselves carry a significant radiation risk, and have been shown to increase the chance of developing other malignancies.

The ability to detect, or rule out, early stage lung cancer without surgery or excessive radiologic scans could dramatically change the current methods of diagnosing lung cancer, and could improve overall survival in a group of patients whom often are diagnosed too late for an effective cure.

U-M cancer scientists are nationally known for their work in identifying circulating tumor cells (cells that have detached from a cancerous tumor and circulate in the bloodstream), particularly in breast cancer research. Now, our team is looking to employ this groundbreaking work in the study of lung cancer, which has opened new possibilities for screening, prognosis, and treatment monitoring.

Circulating tumor cells have been found in the peripheral blood for a variety of solid organ tumors, but until recently these cells have only been detectable in patients with advanced cancers. New technological developments have significantly improved the ability to detect circulating tumor cells and now hold new promise for detecting early stage lung cancers.

Specifically, U-M thoracic surgeons hope to evaluate this new technology using blood samples from current patients with early stage lung cancers. The results of this research will allow scientists to further characterize early-stage tumor cells and the marker proteins on their cell surface which differentiate them from cells in non-cancerous nodules or lesions. Ultimately, if successful, this research could lead to a diagnostic blood test for early stage lung cancer, allowing patients to avoid unnecessary surgeries to rule out cancer and potentially could offer an alternative to CT imaging for at-risk populations.