

Lung Cancer Research: From Prevention to Cure (Video Transcript)

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Dr. Vokes, thank you very much for those kind words and also I wanted to welcome everyone as well. This is Lung Cancer Awareness Month and we're just getting to know everyone with lung cancer, families that have been affected with lung cancer, of course, patients and all the health care providers as well that are taking great care of lung cancer patients. And for today and this week, we wanted to give you a flavor of the research that goes on behind the scenes, in the front scenes as well, in the context of lung cancer and it takes a lot of people to be able to do this. And I actually wanted to thank the whole organizing committee for putting this together and that especially includes Olivia Zatil, Paul Butera, as well as Yolanda Davis, Eileen Lawry and many others who have actually organized this to be able to come to fruition.

And for today, I wanted to give you a brief introduction for lung cancer itself, but at the same time what we can do in the context of prevention for lung cancer as well as therapy for lung cancer, as well as what the future holds for lung cancer itself.

As you all know lung cancer is one of the most common cancers worldwide. There will be over 170,000 patients that will be diagnosed with lung cancer alone in 2006 in the U.S. There will be over 160,000 deaths from lung cancer in the year 2006 in the U.S. alone and about 75-80% of lung cancers are associated with smoking. However, it's very important to realize that over 50% of the patients have stopped smoking and over 15-20% of our patients have never smoked whatsoever.

And so for lung cancer, as you all know, much more research is needed. I don't think we've placed enough emphasis on research in lung cancer like we do for breast cancer, like we do for colon cancer or prostate cancer, leukemias, lymphomas and other carcinomas and hematologic malignancies, but it's really important to realize that we need to invest in lung cancer research because every three minutes someone has been diagnosed with lung cancer. Men have a lifetime risk, one in 13 and women one in 17 of developing lung cancer. But what the horrendous statistics are that at least for the year 2003, which also holds true for 2006, is that the federal government spent over \$14,000 per breast cancer death, over \$10,000 per prostate cancer death, but only about \$1,600 per lung cancer death. Even though it's the most common cancer there is, we're not investing enough money into the lung cancer research field.

But what we also know is that the diagnosis of cancer is quite important. It would be nice to develop tests that can detect lung cancer at an earlier stage. In the traditional days, especially in the context of our clinical acumen as well as taking care of patients, one can look for signs and symptoms of lung cancer. Some of the signs and symptoms include coughing. Every once in a

while you can have blood, coughing up of blood. One can also have fevers or weight loss or facial swelling in the context of superior vena cava syndrome or pain and other organs that might get involved that can give you signs and symptoms.

The most commonly used scans used to be chest X-rays. However, we identified that in the chest, X-rays were not that powerful in detecting small nodules within the lung. So CT scan and PET scans have actually superseded them, but at the same time what we can say is that even though the CT scan/PET scan can detect a 10 mm or 1 cm nodule, less than 1 cm is more difficult to detect at times and we need to be able to have better tests as well. So some of these tests can include a blood test. As you know, we have a blood test for prostate cancer such as PSA or for ovarian cancer such as CA125, but we really don't have any blood test for lung cancer itself and I think we need to do a lot of research with respect to that. One can also do bronchoscopies, and there are traditional bronchoscopies where one does simple biopsies or one can also do fluorescent types of bronchoscopies or GPS types of bronchoscopies that you've heard in earlier lectures this month which can actually detect and diagnose lung cancers at an earlier stage. Of course, the role of biopsies is quite important. If you take biopsy of a large chunk of a tumor, do you take only a few cells and can you detect the lung cancers within a few cells, becomes very important for us and for our patients.

Here are some examples of a CT scan as well as what's important on the PET scan and you can actually appreciate that the PET scan picks up the lesion that you see in the posterior of the lung. At the same time you can detect this by bronchoscopy as well and you've actually seen that during our radiology lectures as well as our pulmonology lectures and you're welcome to download those off of the internet as well at any time. But what we want to be able to emphasize for today is that even though we can detect lung cancer, at many times it can be at a later stage. We want to be able to diagnose lung cancer at a much earlier stage so that the prognosis becomes a lot better.

Some of the studies that are ongoing here at the University of Chicago as well as many centers in the United States as well as across the world is to be able to look at radiological scanning and some of these prototype radiological scanners, can even detect a very small 1 mm resolution of a nodule and it can look deep inside within the lung. Here you see the lung, but these kinds of images can actually show you the lung images much, much better so you can detect the tumor at a much earlier stage itself.

How do you study lung cancer? I didn't come here to talk to you about the pulmonary aspects, I didn't come here to talk about the radiological aspects, but to be able to say that we all work together. But can one study lung cancer within the laboratory itself, as well to come up with better therapeutics, better screening strategies, better prevention strategies? The answer is yes. Even though we don't get as much research funding for lung cancer as we do for other carcinomas or other cancers, we know that we can study lung cancer in a very systematic fashion. So one can do microscopy, one can also do cellular biology or genetics and proteomics, and these are some of the examples I want to share with you for the next few minutes itself.

Actually, this is a gross anatomical picture of a lung cancer, that's the white tumor that you see that's around the trachea and that's what many people biopsy itself.

So what does the biopsy show? In a traditional immunohistochemistry or in a traditional H&E style, what we can see is that the small cell lung cancers look like a small blue cell tumor. Here is an example of two of these small blue cell tumors, and you can also appreciate that there are some crushed artefacts that can happen in these small cell lung cancers. And in the inset it's shown that small cell lung cancers can also be of neuroendocrine differentiations themselves, such as chromogranin or synaptophysin or neuron-specific enolase, but this is really histology. This is what has been going on for over 100 years to be able to diagnose lung cancer by looking under the microscope. Now, I think we need to go further and try to identify what kinds of cancer these are

by diagnosing them on a molecular level itself.

Here is an example of non-small cell lung cancer. As you know, there are many varieties of non-small cell lung cancer. One can have adenocarcinoma, so as an example, small cell lung cancer occur in about 14% of patients with lung cancer. Non-small cell lung cancers occur in about 80-85% of all lung cancers. And of those in the United States, adenocarcinoma make up about 40% of the tumors, and you can see that on the left top panel.

You can also have squamous cell carcinoma, which makes up about 30% of all non-small cell lung cancers or large cell carcinoma or large cell carcinoma with neuroendocrine differentiation, as well as what the right panel shows. It's a subset of an adenocarcinoma called PAC or bronchoalveolar cell carcinoma. And they do tend to behave differently and our therapeutic approach is different as well.

What I want to emphasize here is that even though we can look at these under the microscope, they all behave differently in different patients themselves, so we have to be able to understand that. So how do we understand that? Here are some of the ways we can do that in the laboratory.

Here is a timed life sodium microscopy that can actually show that indeed you can have these normal cells and you can observe the movement of these normal cells over a course of time. And about 180 minutes of real time is about 10 seconds of tape time. And what we've done here is we've actually set up an artificial system within the laboratory where we can study the normal cells. And in the background itself here as an example we can set up really what's important in the context of the lymph node architecture or the lung architecture or the brain environment or whatever environment that we can create. What we also know is that we can take these cells, these normal cells, and we can transform them or make them cancerous. Here's what happens when we take some of the genes that are important in lung cancer. I won't belabor the point in the context of how we identified these genes, but it takes a long time. Sometimes it takes a decade, two decades, three decades to be able to identify the functions of the gene. But if we take these same normal cells, here's what happens.

You can actually appreciate that indeed these cells move around considerably--they are no longer "normal." They have an increased ruffling, they have increased projections, what are called actin-like projections. They also have these tail structures that you can appreciate, but these cancerous cells now also tend to cluster together as well. These are some of the mechanisms of transformation or becoming cancerous, but these are also some of the mechanisms of metastasis. This is how cells can go from the lung into the other organs.

As you know, for lung cancer as an example, lung cancer can go to the other organs, be it lymph nodes or be it the brain or be it the adrenal glands or liver or bone or bone marrow, but cell motility and cell migration are some of the early mechanisms for these kinds of metastasis itself.

Through various cell biological techniques as well as molecular biology techniques, over the course of the past 25 years, many investigators have been able to identify what some of the important genes, what some of the important proteins are in the context of lung cancer.

Here's a cartoon depiction of lung cancer where you can actually appreciate that in the nucleus, this is, for example, the cluster of the cell. This is one of the cells itself, this is the nucleus of the cell. You can have abnormalities of oncogene, so there are oncogenes such as DCL2 or MIC or RAS or her2 nu or EGF receptor which can be abnormal in either non-small cell or small cell lung cancer depending on which type of gene. These oncogenes turn on key mechanisms within the cells for it to be malignant or transform.

Then for every yen there's a yang; so for every oncogene or consideration of oncogenes, there are tumor suppressor genes. And you can see that in the other insert here is that these tumor suppressor genes have to be deleted in the context of lung cancer. So some of the tumor suppressor

genes that get deleted are in chromosome 3P are in chromosome 9P. So it's also these classic tumor suppressor genes like P53 or RB, but they're very important because they get deleted in normal cells and thereby becoming a transformed or a cancerous cell.

Not only can you have abnormality within the nucleus, but you can also have abnormality within the cytoplasm of the cell itself. Here, you can have many signal transduction pathways.

A lot of you may have gone on the internet, a lot of you are already on clinical trials or considering clinical trials. There are many signal transduction proteins that lie within the cytoplasm that can be targeted and this is actually one of the main focuses for us to be able to develop that as novel therapeutics for lung cancer as well as other tumors. You can have abnormalities at the cell surface like growth factor receptors or integrins or adhesion molecules which ultimately signal inside, but they can actually also signal outside, meaning they can interact with the extracellular matrix. That's actually important because interaction with the extracellular matrix can lead to early mechanisms of metastasis. Cell motility, those abnormal cells you saw earlier, interact very importantly with the extracellular matrix to go to the blood vessels, thereby metastasizing.

What are some of these important molecules? Why do we consider them important? Certainly, they turn on key mechanisms of transformation, cell growth as well as early migration or metastasis or invasion of the tumors, but we also know that a lot of genes can become abnormal by being mutated as well. Here are some examples that have been going on through our laboratory for over 17 years now where one can look at various receptor tyrosine kinases or tyrosine kinases which are important functional molecules within the cell or that span the cell membrane, so EGF receptor, for example, and you know Dr. Hoffman talked earlier about Tarceva or erlotinib that targets the EGF receptor, but at the same time the EGF receptor can be mutated and it be mutated within the tyrosin kinase domain which is the enzymatic domain of this receptor which becomes quite important in sensitivity to the drug as well as resistance to the drug. But we also know that there are other receptor tyrosine kinases or other genes that can become mutated or abnormal in lung cancer. As an example here, the erb2 gene, which is important initially was shown as her2 neu in breast cancer, but it can also be mutated sometimes in lung cancer. What we've recently shown is another gene known as cMET receptor tyrosine kinase that's at the bottom panel that can become mutated in various domains themselves.

These can become useful tests in terms of potential hereditary risks at times, potential sensitivity to the medications, potential resistance to medications themselves and these are some of the ongoing studies that we're doing currently here as well as throughout the world as well.

How can you detect these genetic abnormalities? How can you study proteins? You really have to work very hard at it. You can do this in the laboratory with cell lines and that's actually very easy, but many times the cell lines don't tell you enough information about what's going on within an individual person, within an individual tumor itself. What one can do with the various technologies that have been developed is to look at microscopic tissues. Here's an example as you can see, what we can do is the laser capture of microdissection. These are just millimeters of tumors, very small tumors that one can look at under the microscopy in the before and then what one does is uses the laser capture microdissector to take out a very small chunk of the tumor that's actually not visible to the naked eye, but only microscopically and then take it out. But when you take it out, you can actually appreciate that the architecture of the tumor is still preserved and that's actually shown under the microscope here, and you can then stain it. As you can see in the inset, you can stain it for the various receptors. For example, the gene and the receptor I talked about, the EGF receptor, that's seen in the inset and that has a brown staining itself, but you can look at many, many tyrosine kinases, many signal transduction proteins and be able to identify what abnormalities can occur even in a millimeter of a tumor. This is incredible technology that's being used currently and that will get perfected over the next few years as well.

Taking this from one of our patients as an example, of course, with IRB approval and IRB approved protocols, we were able to look at the genetic sequence of that small tumor tissue and this genetic sequence I show you at best is DNA. This is not meant to be a review of molecular biology and don't worry there's no test at the end either, but at the same time I'm going to give you a flavor that you can do incredible genetics and incredible sequence analysis of even a very small piece of tissue and we were able to identify, for example, for this individual and actually help this individual decide on what therapy one could consider an effective therapy. You can appreciate this L858R as well as the E884K, which are some of the mutations that were identified in this particular gene itself.

But can you take this technology to the next level? The laser capture microdissection might take out about 1,000-10,000 cells, but can you do this kind of a technology in even one individual cell? I wanted to give you a flavor of that. The answer is absolutely yes. It takes a lot of dedication, a lot of time and effort, but through a number of investigators working within our laboratories we were able to show that if you take a non-small cell lung cancer, that's the white arrow, that's the large cell you see right in the middle, as compared to a normal leukocyte, we were able to look at the gene sequence of just one abnormal cancer cell and this was actually in the cerebrospinal fluid of one of our patients. Using this technology that has been developed within our laboratories as well as various investigators throughout the country and the world, we were actually able to show indeed that in the non-small cell lung cancer cell, you can actually appreciate that you still have the same mutation that I showed you in a larger number of cells, so this was only for one cell that we were able to dissect out. But then if you look at the normal cell, and I don't show that here, but in the normal cells that we were able to dissect out, we don't see any mutations whatsoever, so this is quite specific to the lung cancer itself.

Can you do this in a high throughput systematic analysis or a high throughput fashion as well? So the answer has become quite clear to us over the past five years is that, yes, but again it takes a lot of resources, it takes a lot of research, a lot of investigators to be able to do this. So here, as an example, I show you this review article from *Nature Reviews Genetics* where you take a punch of a tissue in a paraffin block, that's on the top left-hand panel, and then you make all these cylindrical cores. You can make these cylindrical cores from 60 to 100 different samples and this can be in a very small slide itself that you look under the microscope. Under the microscope then you can dissect out and these are some of these what are called tumor tissue micro rays at the bottom that you appreciate. These are huge number of tumor tissue specimens and then we can look at what proteins can be abnormal, what proteins can be upregulated, what proteins can be down regulated. So systematically then we can say that these are the important proteins within lung cancer or other cancers, but then also therapeutically designed rational targets to bring to clinical fruition itself.

Ultimately our goal is also to understand the mechanisms of metastasis, all those tools that have been developed. Do understand how a primary lung cancer tumor can develop, but as you all know, lung cancer metastases to various organs themselves. So can one study this at the same time? So the answer is yes and usually what you have to be able to do are those time lapsed video microscopies I showed you, those cells that were going crazy once they become transformed or cancerous. At the same time what you can appreciate here is the multifocal, multi-step process where if you take a cluster of tumor cells that's within the lung that you appreciate under No. 1, then what happens is one or a group or a number of cells can break off from the primary cluster or the primary tumor, then prowl along into the extracellular matrix and go on into a blood vessel and then roll along into a blood vessel and then eventually metastasize into the other organs such as the liver as well as the bone as well as other organs within the lung cancer context. I think you can study every one of these steps and we're just beginning to understand all of these steps to be able to

rationally design therapeutics as well.

Based on a lot of preclinical data that goes into drug discovery, we have been able to identify many ideal drug candidates for various tumors themselves. Dr. Maitland will talk about some of these as well and how we can individualize them, but here's a general summary is that you can have No. 1, like growth factor on a cancer cell or growth factor receptors and you all have heard about, for example, EGF receptor in non-small cell lung cancer because erlotinib or Cetuxinab target the EGF receptor at the same time No. 2 is inside the cell or in the cytoplasm for signal transduction molecules. And you can appreciate that there are many signal transduction pathways that one can target and it is quite complex itself. One can also look at other cell surface receptors like gangliosides which are important in small cell lung cancers or go inside the cell again for proteins which process other proteins themselves or look at cell survival pathways as No. 5 shows, or even look at outside of the cell in terms of the tumor stroma interaction, what do the cancer cells interact with in terms of the extracellular matrix or extracellular stromal cells or even angiogenic blood vessels or blood vessels themselves.

As we've discussed over the past month and I think you can download all of these lectures through the University of Chicago Cancer Research site is that we know the traditional therapy for lung cancer can be surgery if it's early stage disease. It can also involve radiation therapy and usually in later stage disease or chemotherapy, if it's early stage disease after surgical resection or in later stage disease even when it becomes metastatic disease and now the role for novel targeted therapies is continuing to be defined as well.

Some of the breakthroughs that have come through various investigators, various laboratories and it takes a lot of time and effort, pharmaceuticals to be able to come up with these breakthroughs in lung cancers themselves but I wanted to recapitulate and reemphasize some of the breakthroughs that have come through from the type of research that goes on in various members laboratories.

As an example, adjuvant therapy in lung cancer has revolutionized our world. About 3-5 years ago we wouldn't have thought about adjuvant therapy after a surgical resection, but now it has become our standard of practice for non-small cell lung cancer. And adjuvant therapy is really defined as treatment, for example, like hemotherapy after surgery to eradicate microscopic residual cancer and prevent cancer recurrence. Five large studies have shown that adjuvant chemotherapy can increase the cure rate in lung cancer.

We also know that for advanced non-small cell lung cancer there are many targeted therapies that have been developed and have been approved by the FDA, but there are many more targeted therapies that are coming to fruition and basically one of the first ones with significance(?) against non-small cell lung cancer that is irisa. We don't utilize this in the United States, but it is still utilized in other countries and it was withdrawn by the FDA in May. Initially it was approved in May of 2003, but withdrawn in July 2005. One can also have Alimta or pemetrexed, which is a folate receptor blocker that was approved initially in February, 2004; erlotinib, which is known as Tarceva, initially approved in November 2004; and the anti-angiogenic, Avastin or Bevacizumab that was just recently approved this year as well. As you can appreciate that we've actually come a long way or as some of us would say, a long way in a very short period of time. But at the same time we have a long way to go as well.

Just to give you some of the examples on how the University of Chicago was instrumental in bringing these drugs to clinical fruition, this is pemetrexed. It's a chemotherapy that was initially approved for mesothelioma and those initial studies were done here at the university and now, most recently for lung cancer in second-line therapies themselves. It's usually given as IV with cisplatin compound, and it's very important for all of us that we don't cause hair loss if we don't have to and this one does not cause hair loss. It was also figured out here actually very intelligently, that you

needed to supplement our patients with vitamins, like vitamin B12 as well as folic acid to have the maximal effect of the chemotherapy and have a minimal effect of the toxicity from this therapy itself.

Erlotinib, some of you might have heard about erlotinib or Tarceva. Some of you might be receiving erlotinib as an active therapy. It's an oral EGF receptor tyrosine kinase inhibitor. It has activity in non-small cell lung cancer even in relapse disease about 10-15% of the tumors will shrink, but actually about 30-40% will be stable. Erlotinib improves the survival in patients with metastatic disease that have failed first-line chemotherapy. Occasionally you may see dramatic and durable tumor responses for this type of therapy itself as well.

Here is the label for Tarceva itself. It targets a receptor found in lung cancer. We talked a little bit about receptor tyrosine kinases earlier. It's taken by mouth, it has less side effects, there is no hair loss, there is no nausea that's usually seen, but one can see a rash like an acne-form type of rash, as well as diarrhea, but these are very easily controllable most of the time.

How does Tarceva work? Basically we've gone over this before, but basically Tarceva binds to the cell surface receptor tyrosine kinase known as the EGF receptor and it blocks its function. The EGF receptor is quite important in driving the cell towards cell proliferation as well as ultimately metastasis. So Tarceva or erlotinib works to inhibit that at the cell surface receptor level itself.

Here's an example of a radiograph where you can appreciate Panel A, this was pre – the lung is supposed to look like that on the right, that is as black surface, but on the left you see it's totally occupied by tumor, but over a course of a few months this patient responded beautifully in the context of this erlotinib chemotherapy that you can see on your left side as well.

There are other mechanisms that one can inhibit in other targeted therapies, so as an example, targeted therapies against blood vessels or angiogenesis is quite important as has been shown by many investigators, especially by Dr. Folkman initially and basically what you can see is that normal blood vessels look like nice, normal, smooth blood vessels, but if you appreciate the tumor blood vessels they look very coarse or they look very ectatic and it's very hard to deal with these ectatic blood vessels in trying to kill off the tumor cells themselves, but based on some of these earlier mechanisms that were identified from the preclinical perspective, that is the research perspective going onto clinical trials as well as then bringing it to standard of practice, you can appreciate the bevacizumab on the left panel is an antibody that targets the ligand for the receptor called the veg-F receptor. It's given intravenously and you can potentially have very major side effects such as bleeding or thrombotic event or clotting event as well as loss of protein in the urine. But there are other medications that are available in clinical trials that are being tested against lung cancer currently, such as sorafenib, and that's a small molecule inhibitor that also inhibits the veg-F receptor, but it can inhibit the other signal transduction molecules within the cell like C-raf that we talked a little bit about earlier in the context of signal transduction molecules.

You can have potential toxicities with this as well, such as skin toxicities or alopecia, loss of hair, or diarrhea. Or you can also look for high blood pressure and that needs to be controlled very well as well.

I'm going to try to end it here and that is to say we're quite excited about the future for lung cancer, but we also strongly believe is that effective research has to be done. We're nowhere near the cure rates for lung cancer as we are, for example, for breast cancer, for colon cancer, for prostate cancer, for leukemias and I personally think that's because we're not doing enough research in this field. So we need to encourage our young minds to be able to do research in this field, but also our older minds to be able to expand the out-of-the-box thinking, to be able to do more state-of-the-art type of research rather than follow the leader, so to speak. In the future we will have routine scans, we will have blood tests for lung cancer, we'll have bronchoscopies and sputum tests, hopefully as

well, and molecular markers that we can detect lung cancer early as well as potentially have family screen. We actually have a high-risk clinic for families here at the University of Chicago if anyone is interested as well, but at the same time we built our high-risk clinic to be able to follow patients who have had previous history of lung cancers or esophageal cancers or asbestos exposures or head-and-neck cancers to be able to detect their cancers at an early stage.

In the future we will have better prevention strategies, we'll be able to diagnose better, we'll have better surgeries, radiation therapy, as well as chemotherapy including novel therapies themselves. I hope I've given you a good flavor of the novel targeted therapy.

I think as one of my heroes has said, "If you want to change the world, be that change." That's by Mahatma Gandhi and I think this is what we have designed here at the University of Chicago is to stamp out lung cancer and let's do it together. Thank you.

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<http://www.uchospitals.edu/specialties/cancer/lung/index.html>

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