

Dr. Thomas Lynch, New Advances and Innovations in Lung Cancer Treatment November 7, 2010 Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson. I am Bruce Barber. Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Francine and Lynn are pleased to welcome Dr. Thomas Lynch. Dr. Lynch is Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital at Yale-New Haven. Here is Francine Foss. Foss I would like to start off by having you tell our audience what it is that got you interested in the study of lung cancer? Lynch I was interested in lung cancer from very early on in my career, principally because of the impact that it makes on patients and families. In the United States, lung cancer is the leading cause of cancer-related death. This year, 180,000 people will be diagnosed with lung cancer and about 145,000 people will die from lung cancer, making it the leading cause of cancer death in men and women. Foss Can you tell us how common lung cancer is around the world? It is very high in prevalence in the United States, but I understand that it is also a major problem in developing countries like China. Lynch Absolutely true, we are seeing much more lung cancer in the developing world. Overall, we expect there will be about 500,000 to 600,000 deaths globally from lung cancer and more than a million cases, and those numbers will continue to go up. Lung cancer mortality and death follows cigarette smoking very carefully. So, in countries where cigarette smoking is increasing, and those include China and India, we are seeing much more lung cancer and therefore, more lung cancer death. Wilson Tom, what sort of symptoms do you see with a patient who has lung cancer? Lynch What is interesting, Lynn, is that lung cancer often presents fairly late in the game. We know that when people have colon cancer they often develop bowel symptoms, or they develop bleeding relatively early before the cancer has had a chance to spread. When a woman has a breast cancer, either a mammogram can pick up an early lesion or the woman may feel a lump when the breast cancer is still very early, but for lung cancer often we do not get symptoms until the cancer has spread and that is what makes it, I think, very difficult to treat. In terms of symptoms, we think shortness of breath is probably the most common symptom in lung cancer patients. Sometimes cough can occur, sometimes blood with that cough, shortness of breath, coughing up blood, and pain can also be a problem, either chest pain or pain in other parts of the body. Wilson What are some of the risk factors for lung cancer? Is it just smoking, or are there other things? 2:50 into mp3 file <http://yalecancercenter.org/podcast/nov0710-cancer-answers-lynch.mp3> Lynch It really is mostly smoking, 85% of the lung cancer in the United States is related to tobacco. What we do know is that there are some less common causes of lung cancer, and asbestos exposure is one of them. Hexavalent chromium, for those people who remember Julia Roberts in Erin Brockovich, hexavalent chromium was the major concern of that movie and then radon is also another cause of lung cancer, but if you take

asbestos, hexavalent chromium, and radon and lump them together, they are still dramatically less than the impact that tobacco makes. Foss Can you talk a little bit about passive smoking exposure, and also about the increasing risk of lung cancer in women? Lynch Two things, passive smoking is clearly a risk for lung cancer. I think it is hard for us to know in any one patient whether passive smoking was a factor in developing lung cancer, but I think one of the most positive things we have seen over the past fifteen years has been the rapid development of smoke-free workplaces and smoke-free bars, restaurants, hotels, and modes of travel, and that is really a reflection of the fact that we recognize that tobacco smoke just does not harm the smoker, but it can harm their family members and people who are with them. There is no doubt that second hand smoke is dangerous and something we should reduce. The second issue is that there is an increased rate of lung cancer in women, two factors there. The first is that women began smoking in very large numbers in the late fifties to early sixties and so we started seeing a spike in cases in the late eighties or nineties with cases for people who started smoking in the sixties. The second is that we believe women can develop lung cancer with slightly less tobacco exposure, so if a man and woman are exposed to the same amount of tobacco smoke, the woman will have a higher rate of developing lung cancer. Lung cancer went from a disease in the fifties that was predominantly a disease of men, to a disease now which is almost 50-50 in terms of its incidence. Foss Is there an increased incidence of smoking in younger people now, and is that pushing the age of onset of lung cancer back to a younger age? Lynch The age of onset seems pretty well established, it is about 67 years old and we have not seen much change in it. People have always started smoking relatively young. If you look at people who start smoking, the typical person starts between the ages of 13 and about 18 years of age and that has not changed much over the past several years. What is disturbing, and it depends upon what survey you look at and what data sets, but frequently studies of the earliest smoking groups suggest that there are increasing rates of smoker in the 15-to 16-year-old age range. Again, some of that may just reflect that we sometimes lose our momentum toward delivering the tobacco message to young people. Wilson What about asbestos, is that a factor? Lynch Asbestos is a factor primarily for people who have occupational exposure, but asbestos causes two types of cancer, mesothelioma which is a cancer of the lining of the lung and that can be a very difficult cancer to treat, and then probably more than mesothelioma it causes non-small cell lung5:59 into mp3 file <http://yalecancercenter.org/podcast/nov0710-cancer-answers-lynch.mp3> cancer, particularly in people who are exposed to asbestos who also smokes cigarettes; if you happen to work at a shipyard, for example, building Destroyers, or building ships, or perhaps in a brake factory where they use a lot of asbestos for brake linings. Remember most of those industry applications occurred in the 50s and by the mid to late 60s and early 70s they were pretty much phased out, but we still do see some people whose asbestos exposure can be traced to very heavy occupational exposure and they get either mesothelioma or lung cancer. Wilson Since these patients sometimes have limited symptoms and present with later stage disease, tell us about how

you actually make the diagnosis. Lynch A lung cancer diagnosis always requires a tissue biopsy, it always requires a biopsy of some abnormal area. Sometimes we can biopsy the lung itself and often we use a CAT scan or sometimes a specialist called a pulmonologist will put a bronchoscope down the airway which is a small, thin, very pliable, scope that allows the doctor, after putting the patient asleep slightly, to go down and examine the airway and biopsy the cancer if they see it down in the airway. We now have a new technique where you can biopsy cancer even if you cannot see it in the area. So between that and CT or CAT scan-guided fine needle biopsy, those are the two ways we diagnose most lung cancers. Sometimes people have lung cancer that spreads to the liver or the brain and sometimes it is through biopsy areas there that we make the diagnosis, but most often it is made by a lung biopsy. Foss That brings up the question of using a chest x-ray to screen patients for lung cancer. There has been a lot of controversy about the use of chest x-rays in patients who are chronic smokers for detecting lesions that may or may not be cancer, and patients undergoing procedures that are unnecessary. Can you talk to us about the role of the chest x-ray and also whether there are any other new screening technologies available for smokers? Lynch That is a great question Francine. In my opinion, chest x-rays clearly do not save lives from lung cancer. By the time you see it on a chest x-ray, almost always the cancer has spread to other parts of the body and so we are pretty confident now that doing screening or routine chest x-rays without symptoms in smokers does not make sense. There is some controversy about CAT scans in this area and there are some people who argue that people who are smokers should have a CAT scan to look for early changes of lung cancer and if you find a spot or lesion on a CAT scan, that's something that you can follow-up with and maybe if you find it early, you can make a difference in how people do. I must say, at this point, we have never proven that and it may well be that we are just picking up early cancers that we would have picked up otherwise and there is a lot of controversy surrounding what you refer to as, cost to patients, in terms of biopsy of things that turn out not to be cancer, meaning people have to go through difficult biopsies and painful biopsies when it turns out to be benign. Unlike a breast biopsy or colon biopsy, lung biopsies carry with them a certain amount of risk, so it makes us a little bit less enthusiastic about biopsying lesions of 9:20 into mp3 file <http://yalecancercenter.org/podcast/nov0710-cancer-answers-lynch.mp3> the lung unless we are very, very worried there may be cancer. I would say at this point there is no hard and fast data that will support doing screening CAT scans for people who are smokers. Foss That would mean that if a patient is a smoker and has no symptoms at all, that you would not recommend going forward with the CAT scan? Lynch I would not recommend at this point going forward with a CAT scan. We just do not have any evidence yet that these have been shown to save lives and there are two large randomized trials which are now going on to try to ask that question and give us some help in terms of telling us whether or not these scans can actually pick up early lesions that can improve survival. What we do know is a CAT scan can find a nodule better than a chest x-ray can, that is not debated, but what we do not know is whether finding those nodules improves survival of patients. That is

very much an open debate in medicine. Foss What about blood tests and looking at the sputum? I know there are lots of molecular tests available now to detect other cancers in the blood and I am wondering if any of those are available for lung cancer? Lynch That's a great question and something which I think we are very eager to see in the next five to ten years. In lung cancer we have made some real strides in understanding the molecular basis of lung cancer, particularly for a never smoker. Yet those understandings have not yet transferred into any early detection test. Our hope is that one day we will be able to do either a sputum test, which means examine some of the phlegm molecularly to see if there are changes within genes of some cancer cells that may be coughed into the phlegm, or even a blood test to look for early changes that could be consistent with lung cancer. There is some work that was done by several groups to look at what are called circulating tumor cells, or cells that are in the blood themselves that are cancer cells, taking those cells out and looking at them and seeing if they are lung cancer cells, sometimes that may turn to be a technology that is interesting down the road. Wilson I know this is a large topic, but let us start to discuss some of the different treatments that are available for lung cancer and what you feel are the advantages to a multidisciplinary approach? Tell our listeners a little bit about personalized medicine. Lynch Lynn, I will break it into two parts, first is a multidisciplinary approach and you are someone who in your own career has made a huge difference for people by advocating strongly for the role of a multidisciplinary approach. What we mean by a multidisciplinary approach is that a patient with lung cancer sees more than one type of doctor. They see a medical oncologist, they see a radiation oncologist, they see a surgeon, they may see a pulmonary specialist if necessary, but they see a team of doctors and it helps them make a decision about what the right treatment for that patient is. For some patients the right treatment might be to do surgery and take the tumor out. For other patients the right treatment might be chemotherapy, so I think it is very important that before a treatment starts patients have the opportunity to consult with a multidisciplinary team. This has 12:24 into mp3 file <http://yalecancercenter.org/podcast/nov0710-cancer-answers-lynch.mp3> made a huge difference in breast cancer and breast cancer really led the way in the multidisciplinary approach. In prostate cancer it makes a big difference and I think we are seeing in lung cancer, certainly in my experience, and I suspect that in yours as well, that it has made a big difference in lung cancer. Wilson Give us some more details about some of the treatment that you do. Lynch Personalized medicine is one of the things you talked about. Personalized medicine can mean a lot of different things, one thing people mean when they talk about personalized medicines is exactly what we just talked about, it is the idea of bringing together a team of doctors that look specifically at a given patient's condition and focus treatment on that given patient, so that is one form of personalized medicine. The second form of personalized medicine is using a molecular understanding of the cancer to be able to inform treatment decisions. One of the things we are working on is taking patient's cancers, once we have done a biopsy, taking a piece of the biopsy, and analyzing that biopsy for the presence of genetic changes that

help predict appropriate therapies. What we have learned over the past several years is that there are several unique genetic changes to lung cancer, something called the EGFR mutation that we look for, there is the ALK translocation, there is the RAS mutation, and all three of those can help us guide therapy and give patients better options. Wilson That is fantastic information Tom. We are going to take a short break for a medical minute. Please stay tuned to learn more information about lung cancer with Dr. Thomas Lynch. Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host Dr. Francine Foss. Today we are joined by Dr. Tom Lynch and we are discussing lung cancer. Tom, let us get back to some of the information that you were discussing before the break about genetic mutations and how that might impact treatment for patients. Lynch Lynn, I think one of the things we are most proud of in lung cancer is that over the past several years we have identified several genetic markers that help explain why certain patients get lung cancer and we have done most of this work in people who are nonsmokers and we now know that there are probably four or five genetic markers that are important. We have learned about something called an EGFR mutation, something called an ALK translocation, and the RAS mutation. Also something called the HER2 mutation. When you have changes in those molecules, what it allows the doctor to do is pick a treatment specifically for a patient with that type of mutation. For example, if you have a patient that has an EGFR mutation, you may pick a drug like Iressa or Tarceva, which is a drug that specifically attacks the Epidermal Growth Factor Receptor. If you have an ALK mutation or ALK translocation, you may go ahead and try a drug specifically targeted toward ALK, a drug such as crizotinib, which is not yet in the market but is in clinical trials. It is an example of how doctors are using molecular information to guide therapy. Now, what Dr. Foss does in lymphomas is we have been using molecular information for quite some time to help guide therapies, and just now in solid tumors, like lung cancer, we are beginning to really understand how molecular correlates can drive treatment. Foss Is the analysis of tissue for these specific mutations available yet to the average patient with lung cancer? Lynch Yes they are, at Yale we have a program for doing molecular profiling of patients with solid tumors with lung cancer, colon cancer, and breast cancer and we are able to molecularly profile these patients looking for a broad range of mutations that can help direct therapy. I think what you are going to see in the next several years is that type of testing platform will become more available at community hospitals and at smaller centers. Right now, the places that are doing the molecular profiling tend to be the larger cancer centers like Yale, Memorial Sloan-Kettering, MD Anderson; the bigger centers are really committed to doing it. Foss If a patient were at a smaller center, a community hospital, say here in Connecticut, and they wanted their tumor to be analyzed, is there a process by which they could get that done? Lynch There are two ways, their doctor could contact us here at Yale and arrange for the sample to be sent and we could run the specimen here or the patient could be referred by the doctor

here to be seen. Either way we'd be delighted to work with doctors around the state to try to increase the number of patients who are molecularly profiled. It is the kind of thing that right now we're at the very beginning of the use of these new tests, but they can have great promise as we go forward.

Wilson What sort of thoughts do you have about how the treatment of lung cancer has changed, say over the last decade, aside from what you have just talked about with the genetic evaluation?

Lynch A couple things, one is we've become more innovative with targeted therapies, which we just talked about, the genetic based therapies, and the second thing is we are becoming aggressive about using targeted local therapies like radiation and radiofrequency ablation to target early lesions. So we have more choices now for treating early stage cancers and I think the third

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big change has been that histology plays a role again. When I was training, it did not really matter if you had adenocarcinoma or squamous cell. What we now know is lung cancers break down into two big types, small cell and non-small cell, and then non-small cells breaks down into three big types, adenocarcinoma, squamous cell carcinoma, and large cell carcinomas. We now know that patients who have adenocarcinoma will do better with certain types of drug treatment and people with squamous cell will do better with slightly different types of drug treatment. So again, I think what we are doing is learning how to get the right drug to the right patient and that is something that is different than it was five to ten years ago.

Foss Tom, in the future do you think patients with lung cancer will not be treated with conventional chemotherapy drugs, the way we know them, or do you think there is always going to be a role for chemotherapy in addition to these other new agents?

Lynch It is a great question. I think we will see chemotherapy around for several more years, but unlike in lymphoma where I think chemotherapy will continue to have a role for quite some time, I think the days of chemotherapy and lung cancer are somewhat numbered, and my hope is that within 15 to 20 years we will no longer be using chemotherapy in lung cancer. I think it will be unusual for a patient to get chemotherapy as opposed to now, where that is still a mainstay of treatment.

Foss Another question I had is, we often times do not focus on the positive aspects of some of these cancers and certainly in lung cancer there are patients that are cured with definitive therapy, although that number is small, could you say a little bit about that group of patients?

Lynch We cure approximately one in seven of the patients who come into our office with lung cancer and by cure we mean that those people live for 10, 15, 20 years and die of whatever they might have died of if they never got lung cancer, and that is a misperception because some people think that you can never be cured from lung cancer. We do have a chance of curing some patients from lung cancer, and those are generally patients who present with good lung function, meaning their lungs are not totally compromised by tobacco and have a lung cancer which can be either surgically removed or could be treated with radiation therapy, and some of those patients also get chemotherapy as part of their treatment. There are some good news stories and I have been taking care of lung cancer patients now for more than 20 years and I have had plenty

of patients who are cured who live 15 to 20 years and the only reason I can't tell you longer than 20 years is because I haven't been doing it longer than 20 years yet.

Wilson Thinking of breast cancer for a second just as a model, there is obviously a lot of publicity, a tremendous amount of fundraising and research being done, which is terrific, but as you have mentioned most of the lung cancer cases are actually caused by smoking and there is some perception that there may be a stigma associated with that. Since it is a different disease where most of the cases are caused by smoking itself, has that impacted potential research funding and the way that perhaps the lay population thinks about the disease?

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Lynch I think you are absolutely right Lynn. I think there is a blame that we see with lung cancer. There is a tendency to blame the patient for developing the disease and therefore, I think lung cancer generates less sympathy from the public. I always have been struck by talking to lung cancer survivors who will very passionately say that no one deserves to get lung cancer. People who started cigarette smoking were using a legal product and they were using a product that has been promoted, encouraged, and enhanced by our society, and therefore, to turn and blame the smoker is unfair and cruel to people, particularly at a vulnerable time in their lives, and so I personally think that is a terrible thing to do, but I also think it explains why people are very hesitant to put direct research dollars into lung cancer. One of the interesting things is that if you go back, and this is not 2010 data but it is 2005 data, if you look at the amount of money that the National Cancer Institute spends per death of a certain cancer, what we find in breast cancer and prostate cancer is that we spend about \$15,000 of research spending per death. In lung cancer, we spend \$1,300 dollars of research spending per death, so big disparities between what's spent per death for lung cancer and then prostate and breast. Now, with that said, I am someone who believes that spending money for all cancer research is good. Meaning, I think that money spent in prostate cancer research and breast cancer research will pay off for all cancer research and I think efforts in lung cancer are going to help women with breast cancer and men with prostate cancer. What I hate to see is different groups pitted against each other as if this was a political race and someone is running for congress. It is not us-or-them. The idea is how we can we fund the research together to decrease the morbidity for cancer, because whether somebody dies of lung cancer, melanoma, lymphoma, or breast cancer, it is the same impact on the patient and family and I think we have to work hard to eliminate cancer death from all causes.

Foss Can you talk a little bit about new developments in the treatment of lung cancer and whether you think that immunotherapies, which are now being used in other types of cancer, will potentially play a role?

Lynch It is interesting that you ask that because we presented data just recently at the European Society of Medical Oncology meeting in Milan which looked at a study that we did examining the role of a new immunotherapy, a drug called anti-CTLA-4 against lung cancer, and really what these approaches are doing is they are trying to turn the body's immune system into an important weapon in fighting cancer and what these molecules understand is that

the way that the body mounts an immune defense is extraordinarily complex and if we can find a way to get these cells, which orchestrate the immune system, to recognize that it is not normal to have a lung cancer, we may be able to lead to regressions of lung cancer. This approach has been proven now in melanoma and we have colleagues here at Yale, Dr. Kluger and Dr. Sznol that have done some groundbreaking work with immunotherapy in melanoma, where these drugs have made huge differences, and this year in our paper at ESMO, we showed that lung cancer might actually respond as well to these drugs. It is a very early study, very preliminary data, but we show that the progression-free survival was longer for patients who are treated with this. We need more data, we need more experience to know if this is a fluke or if this is real, but it was the first time in my experience encouraging that immunotherapy may play a role.25:44 into mp3 file <http://yalecancercenter.org/podcast/nov0710-cancer-answers-lynch.mp3>Foss And again, you would direct the immunotherapy primarily for the earlier stage patients?Lynch Most of the immunotherapy trials have been criticized because they have been done in late stage patients, and we all know that in late-stage cancer patients the immune system is depressed and so I keep an open mind. I think some of these trials will be started initially in late stage patients. I think you are correct that the potential for them is probably greater after surgery or in stage II or III patients, but I would not close the door to the fact that you can have benefit in late stage. You know in melanoma, Dr. Sznol and Dr. Kluger are seeing great benefits even in late stage patients, so I am hopeful we might see benefits in multiple different stages.Foss Is there a vaccine yet for lung cancer, and do you think that there will be one in the future?Lynch There are several vaccines under development for lung cancer and some of those vaccines include taking peptides, or proteins, that resemble proteins that are made by lung cancers, and trying to use those to vaccinate the patients so the patient's body fights the lung cancer. Other vaccines use cells to try to vaccinate the patient against the lung cancer cells and several of those are in clinical trials right now, large clinical trials, where half the people get the vaccine, half do not. And that is an interesting point for patients, because I think a lot of people do not like clinical trials like that where half get it and half do not, but in the vaccine world it's really the only we are going to know whether or not these treatments work as opposed to some of the targeted drugs we talked about earlier where you can give them to a patient with advanced disease and possibly see the disease shrink. In the vaccine world, where disease is gone and you are giving it to prevent recurrence, you almost have to have those treated and untreated groups to be certain.Wilson Getting back to causation and cigarettes, if we did not have cigarettes, at least 80% of the lung cancers would not exist. How are we doing as a society in getting folks to quit smoking, trying to manage that problem?Lynch The smoking rate in the United States right now is about 27% to 28% and men and women appear very similar in terms of numbers. I think that smoking cessation is at the heart of any cancer prevention strategy. We have talked about lung cancer today, but as you know and Francine knows very well, smoking causes head and neck cancer, it causes cancer of the throat and the esophagus, it causes cancer of the pancreas, it causes cancer of the

bladder. There are a broad number of tumors, not to mention stroke or heart attack, so a number of health reasons why we should be working to help patients stop smoking. One of the important quality metrics we are going to be looking at in cancer care nationally is do we advise patients to stop smoking when they get admitted to the hospital? Let's say you get admitted for a broken leg, if you smoke cigarettes your nurses and doctors should tell you that you really should not be smoking and they should offer you quit smoke services and that is one of things we are working on at Smilow and at all the hospitals around Connecticut to try to increase the resources our patients have to be able to stop smoking because it is something which, if you talk to smokers over the age of 20, most people28:58 into mp3 file <http://yalecancercenter.org/podcast/nov0710-cancer-answers-lynch.mp3> want to stop and people who are thirty or older do not want to be smoking two packs of cigarette a day, spending that money, they know how they feel on tobacco. They know it is bad for them. They love their families. They do not want to die. They want to stop smoking and our job is to give them the tools to be able to stop smoking. Dr. Thomas Lynch is the Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital at Yale New Haven. If you have questions for the doctors or would like to share your comments, visit yalecancercenter.org, where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.