



*Welcome to Yale Cancer Center Answers with doctors Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and is an internationally recognized expert on colorectal cancer. Dr. Miller is the Director of the Connecticut Challenge Survivorship Program and is also the author of "Choices in Breast Cancer Treatment." If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or 1-888-234-4YCC. This evening Ed welcomes doctors Roy Decker and Scott Gettinger. Both Dr. Decker and Dr. Gettinger are Assistant Professors at Yale School of Medicine and specialize in therapeutic radiology and medical oncology, respectively.*

Chu Scott, let's start off by discussing why lung cancer is still such a significant public health problem here in the United States.

Gettinger Well, we are still seeing the effects of smoking, even though it has decreased in the last 10-15 years. The incidence of lung cancer might be decreasing a little, but it is still a major problem. Although it is not the most common cause of cancer in the United States, it is the most common cause of cancer death. In fact, if you add up the deaths in a year from the most common cancer in women, breast cancer, and the most common cancer in men, prostate cancer and colorectal cancer, they do not equal the amount of deaths from lung cancer in a year. Lung cancer is generally a cancer of the elderly with a median age of around 70 years. However, I have patients in their 20s who have lung cancer. It affects both women and men, and it affects smokers primarily, but also nonsmokers as well. We think that about 10% to 15% of patients who have lung cancer do not have a history of smoking. There is another substantial part of the population that has a remote history of smoking, so it is still a major problem. Cigarette smoking is down, but it still accounts for over 200,000 cases of new lung cancer a year in the United States.

Chu Roy, let's take a step back and review some of the major risk factors for lung cancer.

Decker Obviously the most important risk factor is cigarette smoking, and not just present smokers, but past smokers as well. Close to half of our patients are not current smokers, but may have quit 5 or 10 years before. I cannot emphasize enough that tobacco history is by far and away the number one risk factor. There are several other risk factors that we do look for such as, radon exposure, chemicals, smoke exposure, second hand smoke exposure, and we are noticing the increasing importance of family history. There are certainly some yet to be determined genetic factors that may predispose people to developing lung cancer.

Chu In the setting where genetics may play a more important role, do we tend to see lung cancer

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present at an earlier age, than say individuals for whom there may be no genetic predisposition?

- Gettinger A family history of lung cancer is not well characterized at this point, so I do not have a good answer for that. I definitely have seen younger patients without a smoking history, and some family history of lung cancer, but I am not sure if we know that yet.
- Chu And what about the issue of second hand smoke? There has been a lot written in the press and it has been talked about in the media, about the increasing importance of second hand smoke. How real is that effect?
- Decker It is hard to say, there is certainly accumulating evidence that exposure to smoke of any kind does present some kind of a risk factor, but if you think about it, it is very hard to go back and identify someone who has never been exposed to smoke of any kind, so the issue is a little hard to parse out.
- Chu Are there any blood tests, or any simple test that can help to make the diagnosis of lung cancer?
- Gettinger No, that is the simple answer. There are a lot of very smart people working on this and some of the people in our own department, such as Dr. Joanne Weidhaas, are looking at some genetic factors that may predispose certain smokers to lung cancer, but there is really nothing out there that is going to tell you whether you are at risk or not.
- Chu On an earlier show, we had Dr. Tanoue and Dr. Detterbeck discuss some of the roles of early detection and screening. For instance, when you have someone who has a very extensive smoking history, you are worried that that individual is at increased risk for developing lung cancer. Are there any diagnostic tests that you might recommend at this point?
- Gettinger No, at this point there is really no role for screening, CAT scans, or x-rays, which are often done in the community. There have been trials to look at this and none of them have been compelling enough yet to support doing this. There is an ongoing trial looking at CT scans versus x-rays in high risk patients. Here at Yale, we are very interested in high risk patients, and we are trying to come up with an algorithm using family history, things that we can find in the blood, or things in the sputum, there is even a breath test we have been looking into a little and what comes out of someone's breath who has a history of smoking. We are trying to put this altogether to figure out who deserves a CAT scan, or some other imaging modality.

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- Chu What might be some of the presenting complaints or symptoms of an individual that has lung cancer?
- Decker Typically you are either going to see respiratory symptoms, someone who perhaps is having a little bit more difficulty with breathing than usual, perhaps they develop a pneumonia, or over several months a history of several pneumonias. Certainly, coughing up blood is something that concerns anyone, but unfortunately, a lot of patients with lung cancer present with metastatic disease. They present with systemic symptoms of fatigue, weight loss and loss of appetite, just a general picture of illness over several months that raises the level of suspicion.
- Chu If any of the symptoms should present themselves, what should an individual do then?
- Gettinger Of course anytime you feel like you are not in your usual state of health, the best place to start is your family doctor. The symptoms that we were talking about are very vague, and there could be a lot of different causes and a very broad based evaluation is the appropriate first step. Ultimately, if you are having respiratory symptoms, then you are going to wind up getting a chest x-ray and perhaps a CAT scan, and that is usually where it begins.
- Chu And then, if there is a mass, or a lesion, that is seen on either the chest x-ray or CT scan, what would be the next step?
- Decker There are two things that we need to do. First, we need to get a diagnosis, a tissue diagnosis. A mass on a CAT scan can be a cancer, but it can be other things as well. It depends on your suspicion. One thing would be a biopsy, unless it looks enough like a pneumonia, then you might want to treat it as a pneumonia, and then repeat a scan, but if you are pretty suspicious, then you might do a biopsy and then you would do other imaging and other procedures to determine the stage, which is very important because it will dictate the treatment as well as give you information about the prognosis. Some of the imaging modalities that we use are PET scans, CAT scans, MRIs, and there are some other imaging studies that we are beginning to look into at this point too.
- Chu The two of you are integral members of the Thoracic Oncology Program at Yale Cancer Center. Can you tell us a little bit about what the Thoracic Oncology Program is and why you feel it is so important to have such a program at the Cancer Center?
- Gettinger It is a really exciting program. We have a multidisciplinary team of cancer experts. As you mentioned, Dr. Frank Detterbeck and Dr. Daniel Boffa are Cardiothoracic Surgeons, Dr. Tanoue is a Lung Cancer Pulmonologist, and Scott and I. There is another radiation

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oncologist as well as a large supporting staff of social workers and APRN's that are very focused around treating patients in a cohesive fashion. The benefit to the patient is that if you come in to the Thoracic Oncology Program Clinic, you then get a very detailed multidisciplinary evaluation. What that means is that a lot of people are sitting around the table together talking about a lot of different treatment options, trying to figure out what is the most appropriate. As medical technology increases at such a huge pace, there are now multiple surgical approaches. There are a lot of different chemotherapies, systemic therapy approaches, and now there are a few different radiation therapy approaches, so each individual patient really needs to be evaluated very thoroughly before any kind of treatment decisions are made.

Chu So are all patients with lung cancer, seen, presented, discussed, and then a treatment plan is put forth?

Gettinger Every new patient that comes to Yale with a diagnosis of lung cancer gets presented in a multidisciplinary tumor board, where, as Roy was saying, we have input from radiation oncologists, pathologists, radiologists, surgeons, pulmonologists, social workers, and a whole host of other folks, and together, we come up with a consensus diagnosis as well as a treatment plan. I can tell you that we often come up with things that you might not expect. We also work very closely with the community, and if a community oncologist has a very complicated case, they will often refer him to us and we come up with a very different diagnosis, and a very different treatment plan. A lot of the molecular studies can be done at other labs, but the question is which test should you do, and how should you use the information? As physicians who see lung cancer everyday, I think we have a better understanding of what these tests mean.

Chu We have an email from Barbara who lives in Orange, Connecticut, and Barbara writes, "I am a 62-year-old woman who smoked for 25 years when I was younger, but now have quit for the last 15 years. Am I still at risk for developing lung cancer, or has that risk gone away now that I have quit smoking for 15 years? Are there ways to improve my health and further decrease the risk of me developing lung cancer?"

Decker First, Barbara should be commended for not smoking for several years, but unfortunately she is still at risk for developing lung cancer. We think the risk is less for those who have quit, and we think the risk is less as the years go by, but as I mentioned earlier, we do see a lot of former smokers, as well as a lot of current smokers, with lung cancer. There has been a lot of investigation into ways to decrease the risk of lung cancer for high risk patients like this, and a lot of it is revolved around antioxidant vitamins. We have just seen the publication of some of that data, it was presented to us at a meeting this year, and

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unfortunately, it does not seem to have decreased the risk of cancer. The reason it has been an area of interest is because we know that smokers have low levels of antioxidants, and so an obvious approach was to try to replace those, or increase those, and prevent the progression of the damage to those lung cells. But unfortunately, we have not identified the right supplement, or we have not identified the right patients, but there are a lot of people working on that right now.

Chu Scott, do you have any thoughts on how Barbara might be able to reduce her risk for developing lung cancer?

Gettinger She has already done it in terms of stopping smoking. Additionally, if she is living with someone who smokes a lot, or she is at work with an employee that smokes a lot, I would try to remedy that as best I can because certainly second hand smoke is a risk factor, although as Roy was saying, a modest risk factor. If she does develop anything out of the ordinary she should start by seeing her primary physician, and he or she can evaluate her further, but right now she has done the most important thing.

Chu Maybe another thought might be just good healthy living in terms of eating plenty of fruits and veggies, green leafy vegetables, and making sure she gets routine physical exercise and trying to keep the weight off, which is going to be very difficult with the holiday season. We are going to go ahead and take a break, and at the other side of the break we will talk more about how we treat patients with lung cancer. You are listening to Yale Cancer Center Answers, and we are here in the studio discussing the treatment of lung cancer with our special guest experts, doctors Roy Decker and Scott Gettinger.

#### *Medical Minute*

*Breast cancer is the second most common cancer in women. About 3000 women in Connecticut will be diagnosed with breast cancer this year, but earlier detection, noninvasive treatments, and new therapies are providing more options for breast cancer patients and more women are able to live with breast cancer than ever before. Beginning at age 40, every woman should schedule an annual mammogram and you should start even sooner if you have a risk factor associated with breast cancer. Screening, early detection, and a healthy life style are the most important factors in defeating breast cancer. Clinical trials are currently underway at federally designated Comprehensive Cancer Center such as the Yale Cancer Center, to make new treatments not yet approved by the Food and Drug Administration available to patients. This has been a medical minute and you will find more information at [yalecancercenter.org](http://www.yalecancercenter.org). You are listening to the WNPR Health Forum from Connecticut Public Radio.*

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- Chu Why don't we pick up and talk about the various stages of lung cancer, because an unfortunate myth out there in the general public is that once a diagnosis of lung cancer is made, that is bad news, the party is over, and the prognosis is extremely dismal.
- Gettinger Well, that is certainly not true. We cure several patients with lung cancer, and we palliate and extend the life in patients with metastatic disease. In terms of staging, there are two general types of lung cancer, non-small cell lung cancer, which is the more common of the two and about 85% of cases are non-small cell, and small cell lung cancer, which accounts for the other 15%. There are other tumors of the lung, which we do not really consider part of lung cancer. In terms of staging, non-small cell lung cancer has four stages, but maybe a better way to think of it is in three groups. You have early stage lung cancer, which is stage I or II, which means that you have a lung lesion with or without lymph nodes within the lung. This is treated with surgery for cure, and in some situations we give chemotherapy after surgery. The second group is locally advanced disease, which means that you have lymph nodes outside the lung, but still within the chest in an area called the mediastinum, and we treat these patients for cure as well with very aggressive chemotherapy concurrently with radiotherapy. Then there is stage IV disease, which means that you have disease outside of the chest, and these patients we treat generally with chemotherapy for palliative purposes, and I think some people have the wrong sense of that word, palliation. It means to improve the symptoms, but also our aim of treating patients with metastatic disease is to prolong their life, and we are doing this because we have better drugs. Our ultimate goal is to turn lung cancer into more of a chronic condition where you use chemotherapy when you need to, and we have seen this. We have had patients live for years with non-small cell lung cancer. For small cell lung cancer, it is pretty simple; it is limited stage, or extensive stage. If you have limited stage, it means that your disease can be encompassed within a radiation field that would not kill you, and we treat these patients for cure with concurrent chemotherapy and radiation. Then there is extensive stage, which is much like stage IV non-small cell lung cancer, which we treat with chemotherapy and radiation for palliation.
- Chu Maybe we can limit our discussion to non-small cell lung cancer, which really is the most common type of lung cancer that we see here in the United States. Roy, obviously the earlier the stage of the disease, the better chance we have to cure patients with lung cancer.
- Decker Absolutely, and one of the frustrations of treating lung cancer is that most patients, unfortunately, present with relatively advanced disease that has either spread to the middle of their chest, or to other parts of their body, but again, patients with disease limited to their chest and to their lungs, very often are candidates for what we call potentially curative

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therapy, therapy that is aimed at eliminating their disease forever. As Scott said, patients whose tumors are limited to one lung are great candidates for surgery, and even patients whose tumors have spread to the mediastinum, or the center of their chest, are candidates for curative therapy with chemotherapy and radiation.

Chu If we have a patient with early stage lung cancer, and the surgeon goes in and takes it out, is there any role for radiation therapy after surgery has been done?

Gettinger We like to consider those cases on an individual basis. For patients with a tumor that is limited to a lung, for example, that has not spread to the mediastinum, we do not think there is any routine role for radiation therapy. Certainly, if the surgical resection was limited, if there were tumor cells left behind, then we would consider some local radiation. One of the other most common indications is patients where we think that their tumor was limited to one lung, but when we go in and the surgery is done we find that they had lymph nodes microscopically positive for cancer in the middle of their chest. Those patients we treat with radiation, and the goal of that is to eliminate any microscopic disease that is left behind.

Chu Do you ever have to worry about the underlying function of the lung before you go ahead and proceed with radiation therapy?

Decker We always worry about the underlying function of the lung, and again, one of the great things about working with a multidisciplinary team is that we get a very thorough evaluation, pulmonary function testing, so we have a pretty good picture of what the lung function is. Unfortunately, most of our patients are smokers or former smokers, so typically those patients do not have the best lung function. Part of the art and science of radiation therapy is trying to eliminate the disease in the patient without causing more harm than good, so we have very complex mathematical models of what lung function is going to be like after we are finished based on what it is like before we start.

Chu And what is a V20 evaluation?

Decker What we look at is volumes of lung that receive a certain dose of radiation, and V20 is one of our little markers. It is the volume of lung that gets 20 Gray (GY), and a Gray is a radiation dose. We look at a lot of little markers, how much lung gets each a certain dose, and as you kind of model this stuff out, you can predict which patients are going to have, for instance, radiation pneumonia, and which patients might have symptomatic shortness of breath after it is done.

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Chu Scott, you mentioned earlier the role of adjuvant chemotherapy, can you expand a little bit on that? When would you consider that? What type of chemotherapy is available currently for patients?

Gettinger For patients with lymph node involvement, we generally use chemotherapy, and it is two chemotherapies. One often being cisplatin, and then you have a choice of another agent, and we generally give it for four cycles, usually every 3 weeks as a cycle, and with these patients, there is no doubt that this improves survival. The absolute improvement is a little different depending on which trial you look at, but I think it is somewhere between 5% and 15% absolute survival advantage with additional chemotherapy.

Chu Is there ever any role for combining chemotherapy with radiation therapy?

Gettinger In the locally advanced setting, in patients who have lymph nodes that are found in the center of their chest, the mediastinum, we approach these patients with a very aggressive regimen of chemotherapy and radiation. We usually will give full dose chemotherapy while they are getting radiation, and this will kill two birds with one stone in the sense that the chemotherapy is radiosensitizing and it actually makes the cancer cells more sensitive to the effects of the radiation, but additionally, we will treat disease that might be outside of the chest, what we call micrometastatic disease, by giving the chemotherapy concurrently with radiation. These patients, depending on different characteristics, we can cure maybe one in five of these patients with very aggressive chemoradiotherapy.

Chu It sounds like the two of you, your two groups, really need to work very closely together to coordinate the chemotherapy and the radiation therapy.

Decker I would guess that Scott and I talk at least once a day on the phone about our various patients. We need to have a back and forth before we decide on the treatment course, because his chemotherapy is going to affect my radiation therapy and vice versa, and of course, we have to coordinate care. While the patient is under treatment for several weeks, or months, we need to take care of the patient together. We are talking about very good and supportive staff, and I think the patient benefits, but the reason the patient benefits is because we talk all the time and we are on the same page.

Chu Scott, tell us a little bit about some of the exciting new advances that have been made in the development of target therapies, certainly for lung cancer.

Gettinger Targeted therapy is somewhat of a misnomer. I think that the implication is that we have a

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chemotherapy which is targeting something, and we distinguish this from more traditional chemotherapy, but traditional chemotherapy does have a target; the DNA, or the mitotic apparatus. In this day and age we have learned more about cancer, and we are taking advantage of that knowledge. We have designed what we call targeted therapies based upon the differences between cancer cells and normal cells. In non-small cell lung cancer there are two such agents that are FDA approved, and there is another one which is most likely soon to be approved. One of them blocks a very important growth pathway in a cancer cell called EGFR; it is called Tarceva, or Erlotinib. The other drug interferes with angiogenesis, and for tumors to grow they need to be fed, much like anything else in your body, and the way anything in your body is fed is through the blood. So, if you were to look at a tumor under a microscope, you would see all these blood vessels that should not be there, and what is happening is that tumor is tricking the body and producing more blood vessels for it, so it can grow bigger and bigger. By increasing knowledge about the mediators of this process, we have developed agents, one of which is called Avastin, or bevacizumab. This blocks one of these key components of this pathway, and this has been shown to improve survival when added to chemotherapy in non-small cell lung cancer. There is a third agent called Cetuximab, or Erbitux, and it is an antibody that interferes with the same pathway that Tarceva does; the EGFR pathway. Recently this has been shown to improve survival when added to chemotherapy in advanced non-small cell lung cancer.

- Chu Are there ways that we can identify which patients might be best suited to receive say Tarceva or Cetuximab/Erbitux versus Avastin?
- Gettinger There are certain clinical characteristics and molecular characteristics that might predict someone to benefit from Tarceva. The clinical characteristics most importantly are patients who do not have a history of smoking. There is an increased response rate in these patients and we believe also increased survival in patients who are nonsmokers. In terms of molecular markers, there are certain things that we can find, mutations in the EGFR receptor, which will suggest a very high response rate. In fact, if someone is found to have such a mutation, we would start with Tarceva very early on in their course, and we would expect a very good response, sometimes dramatic, with complete resolution of all their disease. In certain cases, if we have patients where we might suspect a mutation, we can have their tissue analyzed for it, and if found, then we can prescribe the correct therapy.
- Chu I know that both of you are very interested in developing clinical trials for lung cancer. Can you tell us a little bit about what is going on at Yale Cancer Center?
- Decker I will talk about two upcoming trials that I am developing right now. One that we are very

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excited about is a trial in patients who have metastatic disease. We often treat those patients with radiation therapy to palliate any symptoms they might be having, whether that is shortness of breath, bone pain, or coughing up blood. There is a novel targeted chemotherapy drug that we are going to give to these patients while they get their radiation therapy in an effort to make the radiation therapy work better, and I am excited, because, if this seems to be well tolerated by the patients, and the results are positive, there is a chance we could advance this into patients who are receiving curative therapy. The other trial that I am developing is a trial of what we call radiosurgery. Radiosurgery is an exciting advance in radiation therapy aimed primarily at patients who have early stage disease, and who typically would be treated with surgery. But there are a lot of these patients that are too medically ill to receive surgery because of their emphysema, or other medical problems, so radiosurgery is a way of delivering a very fast and high dose of radiation with minimal symptoms and the cure rate seems to be outstanding. We are actually developing a clinical trial that is aiming to do radiosurgery with less cost in terms of treating the lungs of these very ill patients, so we are very excited about that as well.

Chu Scott, maybe in the last 45 seconds could you tell us about some advances you're excited about?

Gettinger We have several trials available for patients for evaluating traditional chemotherapy in combination with these new targeted therapies that we have talked about, as well as targeted therapy alone, or in combination, with other targeted therapy. In some of these trials we are beginning to see some very interesting results, and all these trials can be found on the Yale Cancer Center web page.

Chu Great, and that is [www.yalecancercenter.org](http://www.yalecancercenter.org). Well, it has been great having you. It is amazing how quickly the time has gone, but we hope to have you back on a future show to hear what is going on in your neck of the woods. You have been listening to Yale Cancer Center Answers. I would like to thank my guest doctors, Dr. Roy Decker and Dr. Scott Gettinger, both members of the Thoracic Oncology Program at the Yale Cancer Center. Until next time, I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

*If you have questions for the doctors, or would like share your comments, go to [yalecancercenter.org](http://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 from Connecticut Public Radio.*