

Dr. Daniel Morgensztern, The Evolution of ONTAK February 20, 2011 Welcome to Yale Cancer Center Answers with Dr. Francine Foss and D.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 chemotherapeutic radiology and he is an expert in the use of radiation to treat lung cancer 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 welcomes Dr. Daniel Morgensztern. Dr. Morgensztern is an Assistant Professor of Medicine at the Yale School of Medicine and he specializes in the treatment and care of patients with lung cancer. Here is Francine Foss. Foss Let's start learning a little bit about you because you are new here to New Haven. Can you tell us how long you have been here and what your role is? Morgensztern That's correct. I am new to Yale-New Haven and just came here in December 2010. I graduated from medical school in Brazil and I trained in internal medicine in Hematology/Oncology in Miami. In 2004, I moved to Barnes-Jewish Hospital in Saint Louis and now I am here at Yale. Foss Well, welcome to New Haven. Morgensztern Thank you. Foss Can we talk a little bit about lung cancer, can you tell us a little about it? Morgensztern Lung cancer is the most lethal malignancy in the world and also in the United States. That means it is the most common cause of cancer deaths. It is also the second most common cause of cancer in both men and women. The American Cancer Society estimates that for the year 2010, there were approximately 220,000 cases of lung cancer in the United States. In the proportion of men and women, it is still more prevalent in men, although the incidences are increasing in women. So, for the year 2010, there were approximately 115,000 male patients with lung cancer as opposed to 105,000 women, so the trend for the incidence will be about the same for men and women in the next few years. Foss Can you tell us a little bit about the age distribution, are we seeing it in younger people? Morgensztern The median age at presentation that we see the most is the patient between 60 years to 70 years, yet we are seeing an increase in the number of younger patients diagnosed with lung cancer, particularly non-small cell lung cancer. Foss That segues into my next question, which is, are there a number of different types of lung cancer? 2:58 into mp3 file <http://yalecancercenter.org/podcast/feb2011-cancer-answers-morgensztern.mp3> Morgensztern Yes. Foss Can you tell us a little bit about the different types? Morgensztern This is a very interesting question. In the past, we used to subdivide them into two main subtypes, non-small cell lung cancer and small cell lung cancer. Now, non-small cell lung cancer has its main subtypes, which are adenocarcinoma, large cell carcinomas, squamous cell carcinoma, and undifferentiated carcinoma. We are now moving towards the subdivision of adenocarcinomas as well, depending on the genetic material in each of the tumors, so we are moving towards more of a subdivision of the lung cancer subtypes. Foss Are any of these types better or worse than the others? Morgensztern Unfortunately, the survival for lung cancer is not very good, yet we have seen multiple advances in the treatment and most of them seem to be restricted to patients with non-small cell lung cancer of the

non-squamous variant. That means patients with non-small cell lung cancer, other than squamous cell carcinoma, which includes adenocarcinoma and large cell carcinomas mainly, particularly for adenocarcinoma, survival is improving significantly recently. Foss Are there any genetic predispositions to lung cancer? Morgensztern Yeah, there have been studies showing genetic predisposition for non-small cell lung cancer. The studies are still very early, but we know there must be some predispositions since there is a higher number of patients that smoke, and not all of them develop lung cancer. There are some recent studies showing some genes that predispose for lung cancer and also genes that predispose for development of lung cancer. We have a smaller amount of cigarette smoking, particularly in woman. Foss Are these genes, genes that we are screening patients for now, or is this all research? Morgensztern No, it is all research so far. Foss Can you talk a little bit about whether there is a propensity for lung cancer in specific ethnic groups? Morgensztern No, there does not appear to be a propensity for non-small cell lung cancer in ethnic groups. The reason we are seeing an increase in lung cancer in women, is because the percentage of women that smoke has been increasing since the 70s and decreasing in men that smoke, so this is the only recent trend that we have seen recently. 5:36 into mp3 file <http://yalecancercenter.org/podcast/feb2011-cancer-answers-morgensztern.mp3> Foss

One of the issues with lung cancer, is that like other cancers if you pick them up early enough, you might be able to do better in terms of caring for patients, is this true? Morgensztern That's correct. That's very important because the earlier you catch it, the higher the chance is of cure, especially if the cancer is in early stage, or early enough for the patients to be treated with surgery, which offers the best hope for cure. Foss What should we be doing to screen patients? Morgensztern That's a difficult question that became even more difficult recently. We have seen lots of trials looking at screening, doing imaging tests in patients before the development of lung cancer to find out the where the cancer could be diagnosed at earlier stage, most of the studies have been negative, but in November there was a study, from which we have only preliminary results showing a 20% improvement in survival for patients screened with CT scan compared to chest radiograph. So, obviously we will have to wait for the final results, but it is intriguing. Perhaps a better option in the future would be to do predicted molecules, either in the sputa or in the blood, which will have less side effects and less radiation from the CT scan, and probably more reliable. Foss Can you talk a little bit about which patients should be screened; obviously somebody who has smoked for a long time should be screened, but what about other people? Say people exposed to passive smoke because their spouse smokes? Morgensztern The national lung cancer threat includes only patients that were heavy smokers or patients that quit smoking less than 15 years ago, so this is the only data that we have. It is a little bit harder to quantify passive smoking, but I think that as I said, if we develop predictive markers, so instead of doing x-rays, CT scan, or PET scans, we can just do a blood test once a year in people that we think are high risk. Also for patients that have mutations, some of them we think may be a risk factor for the development of lung cancer, but

in the future will have a better group of molecules to test that will probably be more reliable than just the history of smoking itself.Foss You are talking about molecules that we can find potentially in the blood that we would use to screen?Morgensztern That's right.Foss Are there clinical trials now that patients could get involved with to look for those molecules or is that available say at Yale Cancer Center?Morgensztern It is not available yet, but I hope it will be available soon.8:23 into mp3 file <http://yalecancercenter.org/podcast/feb2011-cancer-answers-morgensztern.mp3>Foss

When a patient is diagnosed with lung cancer, that often times is based with a biopsy?Morgensztern That's correct.Foss Can you tell us what the next steps would be as far as what kind of a work-up the patient would get?Morgensztern Ideally when the patient has a diagnosis of lung cancer we should look at the staging, which means how far the disease has spread. That would basically guide the way we would treat the patient. In the Yale Thoracic Oncology Program we have a group of specialists from all specialties; pulmonary, radiation therapy, surgeons, radiologists, and medical oncologists and we try to make the decision together. Usually when a patient has a diagnosis of lung cancer, they undergo a CT scan of the chest and abdomen to get an initial idea of if the cancer has spread to other parts of the lung or liver. It is usually followed by a PET scan which looks at the whole body. In some patients what we find is that they may need imaging of the brain, such as a CT scan or MRI and then we are ready to decide how to treat them.Foss Are all patients seen in the multimodality clinic?Morgensztern Yes, we see all new patients in the multimodality clinic. It is very important for all the specialties to give an opinion in a meeting, so by the time we finish the meeting, we know exactly what everybody thinks and we are sure and confident that we are giving the best treatment possible.Foss Let's go back a minute to the presentation of lung cancer, are many of your patients asymptomatic? What are the most common symptoms that they come in with?Morgensztern Unfortunately a small percentage of patients are asymptomatic and have the diagnosis for other reasons such as they fall or have a car accident and the x-ray will show us that. Most commonly, patients present with shortness of breath, chest pain, or worsening cough, or sometimes coughing blood. Occasionally, the patients present with symptoms of spreading of the disease that could be bone pain or headaches, and that is usually a poor sign, a bad sign when they present with distant spreading.Foss So, if you are out there listening to the show and you are a smoker, what are the signs that you should look out for that would make you want to go to the doctor?Morgensztern Most smokers, especially heavy smokers, have a disease called COPD (chronic obstructive pulmonary disease), so they usually have cough and shortness of breath, but you should be careful11:00 into mp3 file <http://yalecancercenter.org/podcast/feb2011-cancer-answers-morgensztern.mp3>

if the cough gets worse, especially if there is a new pain or you are coughing blood, you should seek your doctor immediately.Foss Can you talk about the actual diagnostic biopsy, are patients mostly getting needle biopsies or are they having surgical biopsies?Morgensztern The place of biopsy would depend on the presentation, the location of the tumor. If it looks like from

the CT scans that the tumor has spread to the liver, for example, it is easier to do a biopsy of the liver, which would not only diagnose the cancer, but also evaluate whether it has spread or not, but for the patient that has the disease localized to the lung, it all depends how close they are, either to the chest wall or the main airways. If facing close to the main airways, we typically do a bronchoscopy or needle biopsy, and if it is closer to the chest wall, we would try to do a CT-guided needle biopsy. The patient goes to the CT scan machine, and that would help the radiologist guide where the biopsy should be, which is over the skin.

Foss How often does a patient with lung cancer actually go to the operating room to have part of the lung taken out, is that a common procedure now?

Morgensztern No, this is not common. Nowadays, it is not very common for a patient to require that. Sometimes when the tumor is very small, the service may elect to remove it, so they will be doing a treatment and diagnosis at the same, but for most of the cases either a needle biopsy or a bronchoscopy with biopsy. Bronchoscopy is when we put a camera down the throat and the camera will guide where the biopsy will be, and that is usually enough for the initial diagnosis.

Foss Dan, now that we are doing a lot of chest x-rays on patients, we have been seeing these pulmonary nodules coming up and the controversy has always been, what you do with these pulmonary nodules and how often do those actually represent lung cancer. There has been a lot of controversy about how to handle that. Can you let our listeners know what the recommendation is now?

Morgensztern What you are describing is what we call the single pulmonary nodule and it is hard to know on the first imaging test whether they represent a malignancy or not. There are some characteristics that we look for in that. The first characteristic is whether they have a previous x-ray which showed the nodule to be the same size, so this is usually a good sign, where another nodule, larger than 3 cm, or they are rapidly enlarging, would be a red flag that something must be done about it, usually a biopsy, but it is not known what percentage of nodules represent cancer or not. This should be taken very seriously, at least in the first imaging studies.

Foss We are going to have to take a break for medical minute right now, when we come back we will

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talk a little bit more specifically about some other new treatments for lung cancer. This is Dr. Foss with Dr. Daniel Morgensztern.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined today by my guest Dr. Dan Morgensztern and we were discussing the topic of lung cancer. We talked a little about how lung cancers present in the fact that many patients will have a biopsy and staging studies, from that point, what happens next and what are the treatments for lung cancer?

Morgensztern Once the diagnosis and staging are made, the treatment would depend on the type of cancer and the stage. So, for a small cell lung cancer, which represents only about 15% of the total number of lung cancers diagnosed in the U.S, we have a very simple staging classification, either they have spread or they do not have spread. If the cancer is localized to the chest, we typically give a combination of chemotherapy and radiation, and this is a curable disease. Unfortunately, once the disease has spread beyond the chest

or the thorax, the disease is incurable, so we would try to give chemotherapy which usually is effective and improves survival and quality of life of the patient, so we will try to offer that to the majority of patients. For non small cell lung cancer, the staging is a little more complicated since we have a four stage classifications, but in general, for the patient that has stage I or II which are early stages, we tend to offer surgery. If surgery is not possible, we have new techniques of radiation therapy that are very effective, such as stereotactic body radiation therapy which is a specific type of radiation that focuses on a small section of the lung, so it encompasses all of the cancer and very little of the adjacent lung, and this has been very successful for tumors that are smaller. The patients that have stage II usually means involvement in one of the lymph nodes close to the lung, and we tend to offer chemotherapy after the surgery; we call this adjuvant chemotherapy. Patients with stage III, that usually means that there is an involvement of a lymph node between the lungs, or a mediastinal lymph node. We tend to offer chemotherapy and radiation also with curative intent, we try to cure those patients, although the cure rate is about 20%, there are some cures, and we try to give them this opportunity. For patients17:47 into mp3 file <http://yalecancercenter.org/podcast/feb2011-cancer-answers-morgensztern.mp3> with stage IV, it means that the tumor has already spread. There are some exceptions where we can try to do surgery, for example, if there is only a small lesion in the adrenal glands or in the brain or in the other lung, we can still try to perform surgery of curative intent and we are trying to cure them, but if the disease spread beyond that, where there are multiple lesions, we would tend to give chemotherapy. Just like a small cell that has already spread, the chemotherapy is given with the intent of improving the survival and improving symptoms so patients may live longer and better.

Foss Can you talk a little bit about the side effects of the chemotherapy that you are using?

Morgensztern This has improved significantly since the 1990s. The chemotherapy that we are using now are as effective, if not more effective, and they cause less side effects, especially now that we have better medicines for side effects as well. Most of the medicines will cause nausea, the majority of them will cause hair loss, which we call alopecia, and one of the most serious side effects is a drop in the blood cell counts, so patients may unfortunately be at risk of infection if the white cells go too low, but we do have medicines now that can prevent it, not 100%, but it decreases the chance of those complications from happening. We also have very good new medicines to help for nausea and vomiting, so we have improved significantly recently.

Foss Are there complications associated with the radiation therapy?

Morgensztern Radiation therapies are also improving, but we still see complications. For patients that have, for example, involvement of the lymph nodes in the mediastinum, when they undergo radiation, they also involve the esophagus, so they can have trouble swallowing in the beginning of the treatment or towards the end of the treatment. After two weeks, the majority of patients improve without problems after that. It can also cause what we call pneumonitis, which is the inflammation in the lungs, but all those complications have improved. The probability of having those is decreasing overtime with better techniques.

Foss

Do you think, overall, that the chance of a patient with lung cancer living today is better than say it was ten or fifteen years ago? Morgensztern The probability of a patient for any stage to be living now, compared to 10 to 15 years ago, is much higher, although for patients with early disease that are treated with surgery, the difference is not that great, but for patients with more advanced stage, there is a clear improvement in survival. Foss For many years, there really was no good news in the story of lung cancer, but recently we have had a number of new and exciting drugs and targeted therapies, could you talk a little bit about that? 20:58 into mp3 file <http://yalecancercenter.org/podcast/feb2011-cancer-answers-morgensztern.mp3> Morgensztern With pleasure, we always like to give good news. And even before that, we conducted a study with 130,000 patients diagnosed with non-small cell lung cancer in the United States, outpatients with stage IV, which means that it has already spread to other organs, and we have seen that there were no improvements in the mid 90s to the late 90s, yet in the beginning of 2000, there has been a significant improvement in survival especially for patients of adenocarcinoma for which most of the new treatments work. We have been very fortunate to have medicines approved by the FDA in the mid 90s such as paclitaxel, docetaxel, vinorelbine, gemcitabine, and this was very significant for the care of patients. They improved the response rate, they were less toxic so they cause fewer side effects than the previous medicines, and then in 2000, we have seen the development of targeted therapies. We have seen the EGFR tyrosine kinase inhibitors, erlotinib, and gefitinib. We still use erlotinib now, which has a brand name of Tarceva, which is just a pill that helps some patients significantly. We have seen the development and approval of a drug which improves survival when added to chemotherapy compared to chemotherapy alone. In the last year we have this brand new medicine called Crizotinib, which works only for patients if they have a specific mutation called ALK mutation. This mutation is present in about 4% of the patients with non-small cell lung cancer, usually patients with adenocarcinoma subtype, and all patients should be tested for it because if they have the mutation, they may derive significant benefit from it. Foss All of these are specific targeted therapies that are targeting specific pathways or genes in the tumor cells. Morgensztern That's correct. All of them are specific targeted therapies. Those are the ones that have been approved by the FDA. Now, what we have seen over the last two years is a multitude of new medicines, most of them are tablets which are easier to take that target multiple factors and some of them in early studies have shown results. The main task is to find out which patients have which characteristics, and predict for the response for patients with similar characteristics and who should receive this medicine. There are so many new medicines; we just don't know right which patients to give which medicine to. Foss I guess that is a good problem to have at the end of the day, too many medicines. Can you talk about issues of looking at tumor tissues to try to identify personalized medicine or to try to identify which pathways are activated in which tumors and how you use that information in the clinic? Morgensztern This is the future of medicine, the future of oncology for sure, and this is the main goal of all treating oncologists worldwide. We want to be able to look at the tissue,

look at which abnormality each patient has and provide the medicine that will target the specific pathway. This is what we call personalized medicine, the right medicine for each individual patient. Right now we don't have that much information, we have some mutations that we know could be targeted by specific medicines and outpatients should be tested for that and there have been several24:46 into mp3 file <http://yalecancercenter.org/podcast/feb2011-cancer-answers-morgensztern.mp3> studies in multiple institutions of what we call a whole genome sequence, so the whole genome of the patients is being evaluated and there are mutations being found, the only problem is that we don't know which mutations are what we call passenger mutations, they are there but we don't know if they have any consequence, as opposed to the driver mutations, that are thought to induce cancer. At some point, we will be able to sort it out not only in lung cancer or adenocarcinoma, but we will probably call them non-small cell lung cancer, adenocarcinoma, plus something, this plus something will be whatever mutation is present and whatever pathway is abnormal for which we will have a specific medicine.Foss It is interesting because 15 or so years ago, there was pretty much one formula for lung cancer, everybody got the same two drugs, and now we are basically developing our strategies as we go along and treatments are going to be highly individualized.Morgensztern We hope so. Obviously, it was much easier to practice a few years ago because we had only a few chemotherapies to give and we had been doing this mostly blindly, we just gave it to everybody and hoped some people would benefit, but this is now changing, and we have seen from some very basic information, for example, patients with squamous cell subtype of non-small cell that don't respond. We know that they do not respond to a very commonly used medicine called pemetrexed, so negative selection. If we can avoid giving this medicine to patients that we know would not respond, that would increase the probability of the patient responding to other medicines, or preventing them from having this medicine that would not work, and we did not had this information before.Foss Since there are so many patients out there with lung cancer, the impact of oral therapies is probably most pronounced in this setting, can you talk a little bit about how you see the impact of these oral therapies in terms of the concept of patients say living a normal life with their cancer and not having to run into their oncologist's office all the time?Morgensztern There are good and bad things about oral therapy. There are some oral chemotherapies that are very toxic. The fact that the medicine is oral does not mean it is less toxic, but now with the development of new oral targeted therapies, it's a different story because they cause much less side effects, less nausea, people don't lose their hair, blood counts don't go too low, so we are not so worried now with these meds about a bad infection which could be lethal. It is much more convenient as well, though most of the treatments for non-small cell lung cancer or even small cell lung cancer are given every three weeks, it is much easier for the patient to take the tablets and it will be more flexible for them to schedule appointments to the doctor. It is a very very good advancement and we are welcoming the news.27:50 into mp3 file <http://yalecancercenter.org/podcast/feb2011-cancer-answers-morgensztern.mp3>Foss Can you let us know what you think the

important questions are and areas that should be researched further in lung cancer?Morgensztern On one hand it is very encouraging that patients with adenocarcinoma are having such a significant improvement, and on the other hand we need to develop better therapies for patients with small cell lung cancer and also squamous cell. There are still a large number of patients that we most definitely need to find treatments that will work for this population as well.Dr. Daniel Morgensztern is an Assistant Professor of Medical Oncology at Yale School of Medicine If you have questions 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.