

Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



Hosts

Anees Chagpar MD
Associate Professor of
Surgical Oncology

Francine Foss MD
Professor of Hematology

Steven Gore MD
Director of
Hematological
Malignancies

Pancreatic Cancer Clinical Trials

Guest Expert:
Jill Lacy, MD

*Associate Professor of Medicine,
Yale School of Medicine*

Yale Cancer Center Answers is
a weekly broadcast on **WNPR**
Connecticut Public Radio
Sunday evenings at 6:00 PM.

Listen Live Online at
www.cpbn.org

OR

Listen to Archived Programs at
www.yalecancercenter.org

Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about pancreatic cancer with Dr. Jill Lacy. Dr. Lacy is Assistant Professor of Medicine at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Jill, let's talk first a little about pancreatic cancer, everybody worries about pancreatic cancer, I heard that it is one of the worst kinds of cancers to get, is that true?

Lacy Unfortunately, that is close to an accurate statement. What is pancreas cancer? So the most common type of pancreas cancer, the one that we hear about in the media a lot is officially called pancreatic ductal adenocarcinoma. This is a highly aggressive malignancy that gets it start in the cells that line the ducts of the pancreas and grows from there. About 90% to 95% of cases of pancreatic cancer are pancreatic ductal adenocarcinoma. However, there is a second type that is much less common, about 5% to 10% of cases, that is actually very different, and it officially is called pancreatic neuroendocrine carcinoma, or endocrine carcinoma, and it gets its start in little clusters of cells called islets that are scattered throughout the pancreas. Islets are little endocrine organs, they produce hormones, so pancreatic neuroendocrine carcinomas actually often procedure hormones such as insulin or glucagon which regulate sugar and hormones that regulate our digestion. So pancreatic neuroendocrine carcinoma is much less common and is a very different disease, it is highly curable when diagnosed early and even in patients who have metastatic disease or advanced pancreatic neuroendocrine carcinoma, it tends to have a very long slow natural history. Patients can live a long time with advanced disease, so it is very unusual. Unfortunately, that is uncommon, so the common pancreatic cancer that we all hear about is pancreatic ductal adenoma carcinoma and that is a very aggressive lethal malignancy as you alluded to. I think the statistics kind of tell the story about pancreatic cancer. In the United States in 2014 we are expecting to see about 45,000 cases and unfortunately, the death rate is about 40,000 deaths from pancreas cancer and although it is actually uncommon, only about 3% of all cancers diagnosed in the United States are pancreatic cancer, it is in fact the fourth leading cause of cancer related deaths. It falls behind lung which is at the top of the list, colorectal, and now it is just about even actually with breast for third and fourth place and what is a little disturbing is that in about 10 years it is probably going to move into second place and if there are no advances in the field, in 20 years it will probably be the leading cause of cancer related death. So this is really a huge problem for us.

Gore Is that because the disease is getting worse or because the treatments are better for the other diseases?

3:48 into mp3 file http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers_-_Dr_Lacy.mp3

Lacy I think it is primarily because we have made major strides in treating the other diseases both in terms of early diagnosis with screening and better treatments.

- Chagpar Tell us a little about how advances are being made, because presumably advances are being made in pancreatic cancer to prevent it from getting to that top spot.
- Lacy The two areas where there is tremendous focus right now are in the areas of early diagnosis and screening. The only known cure for this disease right now is surgery and unfortunately only about 20% of patients with pancreatic cancer when they are diagnosed are able to undergo an operation.
- Gore Why is that?
- Lacy 80% of patients are presenting with advanced disease, which is attributed to a couple of features of this disease. First of all the pancreas is what I call a silent organ, it is a big organ that sits way in the back of the abdomen, so you are never going to feel anything. With breast cancer you can feel a lump, you are never going to feel a lump in the pancreas. So the tumor actually has to get pretty large in the pancreas in most cases before it is going to cause any symptoms. The second major problem is biology. This inherently is a cancer that is aggressive and by that I mean that very early on when it is very small it already has spread, or what we call metastasized, to distant sites in the body such as the liver or the belly cavity. So those are probably the two major reasons why it is often diagnosed late. The other problem is that even when it is small there are a lot of major blood vessels that run right around the pancreas. So, sometimes a small cancer will grow around a blood vessel and that is a problem for the surgeon and that would preclude surgery which again is the only known curative treatment. So there is a big focus on early diagnosis and screening even hopefully diagnosing before you have an invasive cancer when it is premalignant, which is a long shot but that is what we are hoping for, so early diagnosis and screening is one area of research and then obviously we need better treatments for patients who present with more advanced disease.
- Chagpar Before we get to, just going back to early diagnosis, if the pancreas is, as you say, a silent organ, how exactly do you do that? Are we talking about yearly CT scans of the abdomen? How do you diagnose pancreatic cancer early?
- Lacy It is a challenge. Right now, none of the consensus organizations recommend any kind of routine screening for pancreas cancer in the general population. Partly because we just do not have an easily validated screening test such as a blood test like PSA or like a mammogram for breast cancer or even colonoscopy, some people would argue that is not so easy, but it is a very effective screening test, and we have nothing like that for pancreas cancer. That is why there is intensive research now focused primarily on looking for a blood test, perhaps looking for pancreas cells circulating in the blood or pancreas cancer DNA in the blood, people are looking at saliva tests so there is a lot of research in that area, but nothing yet. Now there are patients that we can identify who do appear to be at substantially increased risk of developing pancreas cancer and those patients should be evaluated for screening on a case by case basis. The screening modality that

7:36 into mp3 file [http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers - Dr Lacy.mp3](http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers_-_Dr_Lacy.mp3)

we have our imaging tests, MRI and CT scan and also a test called endoscopic ultrasound and that is probably the best way to look for pancreas lesions, precancerous lesions and cancer. Many listeners are probably familiar with endoscopy where the gastroenterologist will put a scope into the stomach,

look for ulcers or inflammation, and this is a very similar test, it is endoscopy with an ultrasound probe on the end of the scope and that allows the endoscopists to do an ultrasound from the inside out of the pancreas and it gives them a very, very good look of the pancreas and they can see lesions that are very tiny and in addition they are able to put a needle into that lesion using the ultrasound to guide them and get a biopsy. It has greatly improved our diagnosis, so that has been a big advance over the last 15 years and that has also greatly improved our ability to get a biopsy which prior to endoscopic ultrasounds was more difficult.

Chagpar So this would be something you'd consider in those people who are at increased risk?

Lacy Yes, absolutely.

Chagpar Who are those people?

Lacy There are a number of risk factors for pancreas cancer that are well identified. Unfortunately getting older is one of them, so about two-thirds of patients with pancreas cancer are over the age of 65, but about 15% are under the age of 55. Smoking is a clear risk factor, I think people think about tobacco and lung cancer and head and neck cancers, but probably about 30% of pancreas cancers are tobacco related. Obesity and a sedentary lifestyle are risk factors for many cancers and clearly a risk for pancreas cancer. Diabetes, so there is a link between diabetes and pancreas cancer, we do not fully understand it, is it the horse or the cart, but I think there is more and more evidence that the recent diagnosis of diabetes or change in diabetic control in a middle aged adult is a risk factor for pancreas cancer. Then folks who have had chronic or longstanding inflammation of the pancreas, called chronic pancreatitis whether it is from alcohol use or gallstones or even inherited pancreatitis, they are at a substantially increased risk. Then there are hereditary cancers. So about 10% of pancreas cancers do appear to be inherited and the most common gene that has been implicated is the same gene that causes breast cancer, the BRCA family of genes, particularly BRCA2. So those patients are at a substantially increased risk of pancreas cancer. There are some other inherited syndromes as well that have been well identified, that are less common than BRCA, and then finally if someone has had a scan for whatever reason and they are found to have cysts, particularly cysts that are full of mucin in the pancreas, that is a big risk factor. Those cysts can be premalignant lesions. So in terms of who should be directed to a program that does screening for pancreas cancer, you look at their risk factors and certainly family history is at the top of the list and then anyone who has been identified to have these mucinous cysts in the pancreas.

Gore So anyone who has had a relative who has pancreas cancer should maybe be screened? Is that right?

11:05 into mp3 file [http://valecancercenter.org/podcasts/2014_0727_YCC_Answers - Dr Lacy.mp3](http://valecancercenter.org/podcasts/2014_0727_YCC_Answers_-_Dr_Lacy.mp3)

Lacy Certainly there should be a discussion and a careful family history in terms of cancer should be taken, focusing on other GI cancers as well as breast cancer and prostate cancer, and if there is any question, a consultation with an expert who is involved in screening for pancreas cancer. Most of the major cancer centers now are offering programs like that.

- Gore And what happens if you have one of these endoscopic ultrasounds and you find a lesion and surprise, it is cancer, I mean it sounds like a horror story to me. What do you do?
- Lacy In screening for pancreas cancer, they are screening for premalignant lesions as well, which is the ideal time to make the diagnosis. Then there is always the challenge of when do you go and do surgery? That is a difficult decision. If you actually identify a cancer, then the next step is to do the work-up and hopefully you will have made the diagnosis in an early stage that the patient will be able to undergo surgery and that certainly will increase the chances for being cured. Unfortunately, of the 20% to 25% of patients that are able to have surgery, only about 20% of those are long-term survivors. So it is more than early diagnosis. We also need better adjuvant therapies to increase the cure rate for those folks who are able to undergo surgery.
- Chagpar Which was the second of the major advances that you started telling us about. Tell us a little bit more about what is going on in the field to really advance the therapies that you have as adjunctive?
- Lacy We will talk about two major advances in the last three or four years for the treatment of metastatic or advanced pancreas cancer. I would say that sort of the underpinnings for any major advances in this disease are going to come from science and research. Understanding the very complicated biology of this disease, which hopefully will give us ideas about more effective therapies, such as targeted therapies or immunotherapies, but that said, the advances in this disease in the last three or four years have come from traditional cytotoxic chemotherapy regimens. As a historical perspective, when I trained a long time ago, about 30 years ago, we had one drug and the average survival of the patient with metastatic pancreas cancer was about three to four months. About 15 or so years ago, there was a minor breakthrough with a new drug approved by the FDA called gemcitabine and that was a very well tolerated regimen that improved quality of life, but only extended survival up to about six to seven months. Now we have gotten the average median survival of patients of metastatic pancreas cancer up to about a year and this has come from these two recent breakthroughs with chemotherapy regimens for treating metastatic pancreas cancer.
- Gore We want to pick that up after the break, but right now we are going to take a short break for a medical minute. Please stay tuned to learn more information about pancreatic cancer clinical trials with Dr. Jill Lacy.

Medical

Minute

The American Cancer Society estimates that in 2014 there will be over 75,000 new cases of melanoma in this country with over 1000 of these patients living in Connecticut. While melanoma accounts for only about 4% of skin cancer cases it causes the most skin cancer deaths.

14:33 into mp3 file [http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers - Dr Lacy.mp3](http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers_-_Dr_Lacy.mp3)

Early detection is the key and when detected early melanoma is easily treated and highly curable. The patients with advanced melanoma have more hope than ever before. Each day patients are surviving the disease due to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments

for melanoma. The goal of the specialized programs of research excellence SPORE in skin cancer grant is to better understand the biology of skin cancer with the focus on discovering the targets that will lead to improved diagnosis and treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR Connecticut's Public Media Source for news and ideas.

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by my co-host, Dr. Anees Chagpar and our guest, Dr. Jill Lacy. We are discussing pancreatic cancer clinic trials. Jill, before the break you were telling us that for patients who have had surgery for pancreas cancer, you have been able to prolong their survival with new combinations of chemotherapy is that right?

Lacy Actually the advances have been in the treatment of metastatic pancreas cancer. Hopefully, those advances will then apply to patients who have had surgery.

Gore Got you.

Lacy In 2010, we learned about a large clinical trial for patients with metastatic pancreas cancer. In that trial, half of the patients received what was the standard of care, the drug gemcitabine and the other half received a three drug regimen, traditional chemotherapy drugs. They weren't new drugs but they were combined together. That regimen is referred to as FOLFIRINOX and the results of that study were really quite stunning. The patients who received the three drug regimen FOLFIRINOX lived nearly a year compared to half a year for the patients who received the one drug gemcitabine. In addition, the quality of life was better, because they were having control of the tumor related symptoms, in particular pain. So that was a huge breakthrough and since that time that regimen FOLFIRINOX has worked its way from cancer centers into the community and is being widely used and without a doubt is changing the natural history of this disease. We have actually seen a few patients with metastatic pancreas cancer treated with FOLFIRINOX who are surviving now to three years. So this is something that we never saw before. That was one major advance. The second advance came last year, again in a clinical trial for patients with metastatic pancreas cancer, half of whom again received the single drug gemcitabine, half received gemcitabine plus a newer drug called Abraxane. This is a drug that is used in breast cancer and very effectively and again what we saw was the patients that received the two drug combination lived longer, not quite as long as FOLFIRINOX, about eight and a half months versus six months. So a very effective regimen as well and so now in the metastatic setting we have two standard multidrug

17:56 into mp3 file [http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers - Dr Lacy.mp3](http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers_-_Dr_Lacy.mp3)

chemotherapy regimens that have improved the prognosis for these patients. Obviously, we would not call this a home run. We do not think we are curing folks, but the patients are living longer buying time and in general they are feeling better during that period of time, because it is controlling the tumor related symptoms.

- Chagpar It seems to me that the FOLFIRINOX story, as well as the Abraxane story, are both stories of why patients ought to participate in clinical trials.
- Lacy Absolutely, we really appreciate our patients who are willing to go into clinical trials. It is often not an easy decision and neither of these discoveries would have been made possible if it wasn't for the patients that went into these studies. This is how we make advances in the field.
- Chagpar Because I can imagine the patients might have looked at you when you were trying to enroll them in clinical trials and saying, why should I take three drugs instead of one drug, even though these are standard chemotherapeutic drugs. Is it really going to make a difference, and yet they had twice the survival.
- Lacy That is correct and so again we really greatly appreciate our patients. We could not make advances like this without their involvement.
- Chagpar So what are the next clinical trials on the agenda?
- Lacy Obviously we have a long race to go. Still only about 5% of patients with this disease are surviving five years. So when you compare this to say breast cancer, which is 90%, prostate cancer is actually 98%, colorectal cancer, about 2/3 of patients survive five years. We have a long ways to go and so progress is going to come through research, understanding the basic biology of this disease, which is very complex, as well as clinical trials. We are actively engaged obviously in that endeavor here at Yale. For example, one of the studies that we have open here at Yale for patients with newly diagnosed metastatic disease is a study where the patients will be receiving FOLFIRINOX and added to that will be a biological agent that is called hyaluronidase. So what is that? It is an enzyme that breaks down the sort of scar like armor that we often see around the pancreas cancer and if you can break that down, the theory is that you will get better penetration of the drugs into the tumor and more effectiveness. So, that is one area of research looking at this sort of scar-like protection around pancreas cancer that has created some challenges in terms of treating it both in terms of drugs penetrating and also creates a hostile environment for the immune system in terms of attacking the tumor. We are also now looking at using these two multidrug chemotherapy regimens in the setting of patients who are able to undergo surgery. The hope is that if we use these more active regimens, either before or after or before and after surgery, that we will be able to increase the cure rate much as we are doing in breast cancer where after mastectomy or lumpectomy most patients or many patients will be getting chemotherapy. So if we can use more effective chemotherapy in pancreas cancer, maybe we can get that cure rate from 20% up to a much higher level. So, we have two studies at Yale looking at that aspect, one is for

21:34 into mp3 file [http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers - Dr Lacy.mp3](http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers_-_Dr_Lacy.mp3)

the patients who already had their surgery and come to us. This is again a randomized trial so sometimes it can be challenging for the patients. Half of them will get gemcitabine after the surgery and half of them will get gemcitabine and abraxane, the two drug regimen and hopefully from that we will learn that maybe two drugs will get that cure rate up higher and then the second study takes a slightly different approach. The patients who present to our surgeons who have localized disease are

able to have surgery are offered the option of getting chemotherapy before surgery and there are a lot of reasons why that may be advantageous in terms of increasing the cure rate and the particular chemotherapy that is a part of this protocol is the FOLFIRINOX regimen so highly active regimen. So they get about three months before surgery, then surgery and then three months after surgery. So those are some clinical trials that we are offering here at Yale.

Gore Does radiation treatment play any role in the treatment of pancreatic cancer?

Lacy In certain situations, yes, where we had used radiation historically has been after surgery. It is becoming less clear over time that that offers much of a survival benefit and that is an issue that has been somewhat controversial, so we are moving a bit away from using radiation after surgery and we are focusing on using drugs. But the one scenario where radiation likely has a very important role to play is in those patients with advanced pancreas cancer who have disease if it is not metastatic, it is localized, but the surgeon cannot do surgery because the tumor is wrapped around the blood vessel. That seems to be a scenario where a combination of the active chemotherapy regimens followed by radiation seems to be extending survival. So that is a situation where we often will use radiation.

Chagpar What about immunotherapy? You briefly touched on the fact that the immune system plays a role. I wonder, especially in pancreatic cancer where they have this scar-like armor, whether immunotherapies have any role or may be particularly active if we can breakdown that scar and help our immune systems fight off these cancers?

Lacy This is a very exciting area of research for pancreas cancer. I think this has real hope for us. So as many have heard in the media there is a lot of excitement about immunotherapeutic drugs for treating cancers. There is a new class of agents called immune-checkpoint inhibitors. These are drugs that modulate the immune system so that it can attack cancer in a very specific way. These drugs have been very successful in certain cancers, most notably melanoma and lung cancer and they are now being evaluated in many other cancers as well including pancreas cancer. We do not know yet how well they are going to work in pancreas cancer but we do have at least one study open at Yale that looks at either one or two of these immune-checkpoint inhibitors in the patients with solid tumors including a cohort of patients with advanced pancreas cancers. So a lot of research is focused on that. Another area of research related to immunotherapies is trying to make pancreas cancer more visible to the immune system by using vaccines. So this is something that some institutions have been focused on for many years, but have not made a lot of progress, although last year, there was an important study that was presented at one of the cancer meetings where, again, this is in patients with advanced pancreas cancer, who went through the drugs,

25:45 into mp3 file [http://valecancercenter.org/podcasts/2014_0727_YCC_Answers - Dr Lacy.mp3](http://valecancercenter.org/podcasts/2014_0727_YCC_Answers_-_Dr_Lacy.mp3)

received either a single vaccine or two vaccines in combination and it looked like the two vaccines in combination were associated with an increased survival. So maybe if we can do a combination of using vaccines to make the cancer more visible to the immune system and then using these immune-checkpoint inhibitors to turn the immune system on, that may be an approach that will yield some progress. This is actually being undertaken at some cancer centers, the combination of vaccines and

these immune-checkpoint inhibitors. So, it is a very exciting area, and I think the jury is still out and we are eagerly awaiting results from some of those trials.

Gore It sounds like somebody with a new diagnosis of pancreas cancer has a long road ahead and a lot of decisions to make, and it must be hard to negotiate I would imagine?

Lacy There are also many challenges to treating this disease as we have been discussing here today. I think it is important that the patients have an interdisciplinary team that is involved in their care, it certainly often will involve a surgeon if they are able to undergo surgery, a gastroenterologist plays a key role. These patients develop a number of gastrointestinal complications from obstruction of their bile duct, obstruction of their stomach, obstruction of their bowel. We need the gastroenterologist to help us manage those. The gastroenterologists are also very involved in the diagnosis. The radiation therapist often has a role to play and of course the medical oncologist in treating the patient's with systemic therapies or drugs. So, I think having an interdisciplinary team is very important. I think navigating the system in terms of clinical trials is a challenge for patients. I think the first place to start probably is with the conversation with their oncologist, should I be looking for clinical trials, at what point should I go to the major cancer center to investigate clinical trials? I think this is the first place to start for most patients.

Chagpar We started this whole conversation talking about dismal prognosis for many pancreas cancers and just a few minutes ago when you were talking about vaccines, do you think that there will be hope at some point for prevention of pancreatic cancers in people who are at high risk? We went through a whole battery list of people who are at high risk and if we are able to find what causes these cancers, do you think we will ever get to a point where we will not have to look at the dismal prognosis because we would have prevented the disease to begin with?

Lacy Certainly where we could make the greatest impact with this disease would be to have some type of preventive therapy and then if we cannot achieve that goal, early diagnosis through an effective screening modality, and so that is why there is so much interest in those two areas. Now in terms of prevention, I think there is a lot of interesting research in that area. I would mention that just over the last few weeks there was an interesting study that received quite a bit of media attention that came out of Yale School of Public Health showing that low dose daily aspirin actually decreases the risk of cancer by about 50%. There is a lot of interest in aspirin as a cancer preventive drug and this is another disease where it may have a role to play. Vaccines, I do not think we are there yet, but certainly I think one can be hopeful that maybe that is the future for this disease.

29:27 into mp3 file [http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers - Dr Lacy.mp3](http://yalecancercenter.org/podcasts/2014_0727_YCC_Answers_-_Dr_Lacy.mp3)

Dr Jill Lacy is Associate Professor of Medicine at Yale School of Medicine. We invite you to share your questions and comments. You can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR Connecticut's Public Media Source for news and ideas.