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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it is a conversation about pancreatic cancer with Dr. James Farrell. Dr. Farrell is an Associate Professor of Medicine and Digestive Diseases at Yale School of Medicine and the Director of Yale Center for Pancreatic Diseases. Dr. Chagpar is an Associate Professor of Surgery and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center. Chagpar James, I thought we would start by talking a little bit about pancreatic cancer. What exactly is it, how common is it, and how lethal?

Farrell Everybody has a pancreas gland. It is fairly deep in the abdomen, behind the stomach. It is quite a difficult gland to get to, and on average, in the United States every year anywhere between 45 to 50,000 people will develop a type of pancreatic malignancy. The most common type is what is called pancreatic ductal adenocarcinoma. There are also some less common forms such as acinar cell carcinoma or endocrine neoplasms of the pancreas, but when we talk about pancreatic cancer, we are typically talking about pancreatic ductal adenocarcinoma and that makes up the bulk of about 50,000 cases or so every year in the United States.

Chagpar Most people who think about pancreatic cancer, I am certain that our listeners will remember some of the people, some of the celebrities who have died of pancreatic cancer, people like Patrick Swayze and Steve Jobs. They did not die well. We were often told in the media that this is an aggressive cancer, is that true?

Farrell It is partially true. It is definitely an issue relating to the aggression of the cancer itself, but also how it presents. A lot of patients with pancreatic cancer present late in the stage of their disease. We broadly talk about an early stage that might be resectable by surgery. The next kind of global type of stage would be what is called a locally advanced stage, where it is involving some major blood vessels that would preclude surgery. And then the other large group or stage is what is called metastatic disease, where it has spread outside the pancreas to involve the liver, for example, or sometimes up into the lung. Currently, only about 15% of all patients with pancreatic cancer present in that early resectable stage and the remainder are kind of evenly divided between locally advanced and metastatic disease. And the reason for that is where the gland is and where the tumors are. Some of the tumors do originate in what is called the head of the pancreas and also in the head of the pancreas is the drainage

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Podcast-Farrell_338358_5_v1.mp3 from the liver. So, when people develop these tumors, they may not have pain per se, but they may go jaundice, they may go yellow because the tumor is obstructing the drainage from the liver and that is often the first symptom that they have or sign rather that they have that there is something going on. And then, several tumors often present out in the tail of the pancreas, which is not really obstructing or blocking anything and they can often present very late in the stage. And so, it is a big problem in terms of presentation. When you are dealing with only about 10-15% of the population who present at a stage that could be potentially resectable by surgery.

Chagpar That is really problematic then. When we think about other cancers where we have certainly made progress – breast cancer, for example, it is all about early detection, it is all about finding those cancers at the earliest possible stage when they are the most treatable. Are we making any headway in terms of early detection in pancreatic cancer?

Farrell I agree with you in terms of there is a lot of emphasis as there should be in terms of early detection with pancreatic cancer. But that is not to say that there have not also been some improvements in the area of treatment, but really the onus is on us right now to improve our ability to detect this early, and we are seeing these in terms of numbers that are out there. When you look at overall incidence of cancers, pancreatic cancer is actually down on the list. When you look at the rates of cancer-related deaths, pancreatic cancer jumps up into the number 4 spot. And it is estimated that by 2025, it may be the number 2, even number 1 cancer-related death etiology, and this is primarily due to a lot of progress being made with other cancers such as you mentioned, breast cancer and colon cancer and really there have been some initiatives in the world of early detection that are beginning we think to bear fruit, and rather than looking at the general population, what is going on is we are looking at particular groups that are felt to be at increased risk for developing pancreatic cancer. And the three broad groups that we look at are things called pancreatic cysts, a genetic or family related risk of pancreatic cancer and then more recently there has been a lot of interest in the realm of diabetes as a risk factor for pancreatic cancer.

Chagpar Let's break that down a little bit. Certainly I think people might know if they have a family history of pancreatic cancer and they hopefully know if they have a history of diabetes, how does anybody know if they have a history of pancreatic cyst that puts them at risk of pancreatic cancer?

Farrell This is the problem, and the vast majority of patients who develop pancreatic cysts, and just to remind everybody, cysts are these fluid-filled balls that lodge in the pancreas, and the vast majority of those are asymptomatic, and they are picked up incidentally when individuals go for CAT scans or MRI scans or abdominal ultrasounds

6:20 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0722-Podcast-Farrell_338358_5_v1.mp3 for often unrelated reasons, so someone

has a kidney stone or a concern about their liver. These cysts are often incidentally found in the pancreas, and depending on who you read and who you believe, the incidence of these cysts ranges from anywhere from 3-4% to about 20-30% of the population. Definitely with advancing age, these cysts become more prevalent. The vast majority of them do not develop into pancreatic cancer and the issue is for us to try and figure out which ones actually do. And we have a variety of ways of looking at people's cysts on their pancreatic scans and/or CT scans and/or MRI scans. A lot has to do with the size of the cyst, the conformation of the cyst and other features that are found on the CAT scan or MRI scan. I have to say yes, they are very common, the vast majority do not ever develop into pancreatic cancer. We have some pretty good guidelines now for following patients who do have pancreatic cysts to decide who should be followed, who does not need to be followed, who needs to undergo additional investigations such as an endoscopic ultrasound to take a closer look at the pancreas, what group of patients need to be seen by a surgeon for consideration for surgical resection. So, we have learned a lot about pancreatic cysts, yes we understand that the vast majority of them never develop into cancer and we are getting better at identifying the ones that do and trying to sub-select them.

Chagpar Let's delve a little bit more into that because I can imagine that there may be listeners who have gone for a scan for some other reason, their gallbladder or their kidney or whatever else and an incidental note is made of a pancreatic cyst, and maybe their doctor said to them, you know your gallbladder is fine or yes you have a kidney stone and really the pancreatic cyst was not something that anybody paid much attention to. Who are the people, if found to have a pancreatic cyst on an incidental finding, on a scan, should be seeking further care, further followup, further surveillance?

Farrell The first thing to say is that everybody should have a comment made about their pancreatic cyst and it is quite alarming when patients first hear that they have something on their pancreas. They have not really thought about that organ at all and the first thing they hear is that "oh! There is actually something going on in your pancreas." I try and reassure people even before we have seen them to say that again the vast majority of these individual cysts will never amount to much, but we have to figure out which ones do. And so, it is very much based on a variety of factors that are actually seen at the time of the CAT scan or the MRI scan. One of the drivers is the size of the cyst. Typically we are not that worried about 1-cm cyst, 1.5-cm cyst, we get a little bit worried at 2 and for sure at 3-cm cyst. But we are also looking for evidence that these cysts have changed from being kind of fluid-filled containers to having a more solid appearance, and often that is something that can be picked up on a CAT scan or an MRI scan. Whenever there is doubt about that or whenever there is doubt about the size or there is something that may be 2.5 or 3 cm or larger, we often ask the

9:37 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0722-

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Chagpar Now, presumably when you say followup, you mean with additional CAT scans?

Farrell Because these patients have cysts that we know are at risk for growing in size and are certainly at risk for developing into a cancer, we have decided that we would like to follow them for a period of time and that typically has involved repeating either an MRI or a CAT scan every year or every other year depending on the initial size of the cyst and then occasionally asking for an endoscopic ultrasound and biopsy for the worrisome cysts.

Chagpar What about patients who have diabetes, that is one of the other categories you mentioned? There are a lot of people in the world who have diabetes, so should all of them be followed, should all of them have some sort of evaluation of their pancreas, what should be the take-home message for our listeners who are diabetics?

Farrell This is an area that is evolving as we speak, and we are very conscious of the fact that there is a large number of diabetics in the population, and now there are studies to back this up, we have noticed that there are certain patients who present to us ultimately with pancreatic cancer and when we talk to them, we find out that they developed diabetes for the first time 6 months or a year or 18 months before they develop their pancreatic malignancy, and perhaps at a time when there was no demonstrable malignancy for example in their pancreas. And it has led to us kind of scratching our heads going, well this is a chicken or egg story, so what happened first, is it because the patient had a tumor in the pancreas and that destroyed the ability to

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Podcast-Farrell_338358_5_v1.mp3 generate insulin, and often that is not the case. There are certainly patients whose diabetes improves after they have had their tumor removed. So, it is still not clear whether it is the diabetes that results in the pancreatic cancer, but there is some thought that maybe there is an early pancreatic cancer, a small cancer that is secreting hormones or what is called a para-endocrine effect and that may be resulting in diabetes. So, this phenomenon has been noticed, it has been studied in relatively large populations and the risk group that we feel is at an increased risk are new-onset diabetics in the middle age, so people around the age of 50 or so and with increasing age, and we feel that the risk of them developing a pancreatic malignancy is probably within the first 3 years after they develop this new-onset diabetes. That is a very alarming statement to make because there is a lot of new-onset diabetics even at the age of 50 or so, but the risk is probably about 1% of that population would go onto develop pancreatic malignancy and we are certainly interested in studying that population.

Chagpar We are going to learn a lot more about early detection of pancreatic cancer, how we diagnose it and maybe how we treat it as well right after we take a short break for a medical minute. Please stay tuned to learn more about diagnosing and treating pancreatic cancer with my guest, Dr. James Farrell. Medical

Minute

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This is a medical minute about smoking cessation. There are many obstacles to face when quitting smoking as smoking involves the potent drug nicotine, but it is a very important lifestyle change, especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments, decrease the likelihood that patients will develop second malignancies and increase rates of survival. Tobacco treatment programs are currently being offered at federally designated comprehensive cancer centers and operate on the principles of the US Public Health Service clinical practice guidelines. All treatment components are evidence based and therefore all patients are treated with FDA approved first-line medications for smoking cessation as well as smoking cessation counseling that stresses appropriate coping skills. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio. 15:17 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0722-Podcast-Farrell_338358_5_v1.mp3 Chagpar This is Dr. Anees Chagpar and I am joined tonight by my guest Dr. James Farrell. We are talking about the diagnosis and treatment of pancreatic cancer, but even before we get to diagnosis and treatment, we are really starting to talk about early detection, and what Dr. Farrell was telling us right before the break is that we think about 3 main categories, those who have pancreatic cysts, often as

an incidental finding on another scan that was done for some other completely different reason, people who are diabetic, particularly those with new-onset diabetes in their 50s and then James, the last big category was genetics. I think a lot of people are beginning to understand that this whole role of genetics seems to be playing a role in many different cancers as we learn more about the human genome and how mutations or mistakes in some genes can predispose people to cancer. So, what is the scoop with pancreatic cancer?

Farrell For a long time people were very appreciative of the fact that family history and genetics played a role for sure in breast cancer and colon cancer, but it is really only in the last maybe 10 or 15 years that the penny has dropped with respect to pancreatic cancer and familial risk. About 10% of all patients with pancreatic cancer have a family history of pancreatic cancer. And that is defined as at least two first-degree relatives with pancreatic cancer. And often until you ask, you do not get the history because people just do not volunteer this information, they have not thought about it or they are more preoccupied thinking about other cancers that run in the family. But we think now about 10% of the patients with pancreatic cancer have a family risk of pancreatic cancer. We still do not fully understand all the genetics or what genes are being transmitted, the most common genetic abnormality that is found in these group of people would be the BRCA-2 mutation that goes along with the BRCA-1, the PALB-2, the ATM mutations. These are genes that are involved in DNA repair and so very intrinsic to cancer development and are associated with other malignancies, such as breast cancer and ovarian cancer and even prostate cancer. And for sure, there are individuals who carry these genes, who have a strong family history of pancreatic cancer. A lot of other issues have been identified. There are some more uncommon types of genes and genetic situations such as Peutz-Jeghers, the P16 mutation and even hereditary pancreatitis. But really the big players in this area are individuals with a family history of pancreatic cancer or a family history and a genetic abnormality such as the BRCA-1 or BRCA-2 mutation.

Chagpar What about all of the patients that I see in my clinic who have a BRCA mutation, but who do not necessarily have a family history of pancreatic cancer? Should those people be followed or screened for pancreatic cancer?

Farrell This is actually a bit of a controversial area and a lot has to do with just how high the risk is, and for sure when you have those mutations and you do have one or two or

18:17 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0722-Podcast-Farrell_338358_5_v1.mp3 three family members, your risk is at a sufficiently high level that it justifies us talking to you about pancreatic cancer screening and asking you to undergo for example an MRI scan or a CAT scan or an endoscopic ultrasound. When we have individuals who have the BRCA-1 or BRCA-2 mutation and do not have a family history, often we are faced with, well if there is not a very extensive family history or if they do not know, we certainly counsel them and right now the recommendations would not favor

them having pancreatic cancer screening, but that may change in the future because it is becoming an issue, especially as more and more individuals are not really clear about their extended family history and as more and more of this genetic testing takes place.

Chagpar And I think another thing that is so important is that oftentimes people will say, well you know my mother, my sister, my brother – someone had abdominal cancer, and it is really hard to know well is that stomach cancer, is that pancreatic cancer, is that colon cancer, is that ovarian cancer? And it seems that that would make a big difference in terms of assessing their pancreatic cancer risk?

Farrell And it does, and I think in the current environment with a very active electronic medical record and ability to get access to those sorts of medical records, it is becoming easier to answer that particular question, but in former times, it was a great challenge and we just did not know. But we do our best to try and get those medical records to try and confirm what exactly is going on in this particular family.

Chagpar And so for these patients who are at increased risk, either because of cysts or because of diabetes or because of the genetic predisposition, is the followup to do that CT scan to try to find these pancreatic cancers before they cause symptoms and before they become locally advanced or metastatic, or are there other modalities that can be used, I mean is there a blood test that can be used to follow these patients?

Farrell To date there is no one single blood test or even stool test that can be easily done in a noninvasive manner to pick out the patients who have either an early cancer or a preinvasive cancer. There are certainly lots of things under investigation. But it is not an optimal time right now for blood tests at least for pancreatic cancer, and a lot of that has to do with the nature of the disease and the difficulty we often have in actually finding preinvasive cancers. We did talk about cysts and cysts are relatively easy to identify and find and often are preinvasive lesions that can develop into cancer. But we suspect that the vast majority of pancreatic cancers in their preinvasive form, the form we would really like to find them at, are very difficult to image. And so, that makes it a challenge when we are studying this and even evaluating patients that are at higher risk. It is a combination of the best tests that are available in 2018 and it is a combination of good quality imaging with MRI scans or CAT scans and then some form

21:15 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0722-Podcast-Farrell_338358_5_v1.mp3 of endoscopic ultrasound to really take a closer look at the pancreas. But yes, as I said before, there are a lot of studies ongoing to try and find a good noninvasive blood test for pancreatic cancer or for a variety of cancers that could be used at once, and we are hopeful that that will help us find the patients that we can look for pancreatic cancer not just in these high-risk groups that we are talking about, pancreatic cysts,

we are talking about family history and diabetes, but even the larger general population who are also very interested in knowing what their cancer risk is.

Chagpar You have mentioned a few times endoscopic ultrasound as a means of taking a closer look at the pancreas and sometimes even being used with biopsy to make a diagnosis, tell us more about how that works exactly.

Farrell Endoscopic ultrasound is a combination of regular flexible endoscopy as well as ultrasound technology. So, the endoscope itself is passed down into the stomach and then a little bit beyond often into the small bowel, and when there, we can look through both the stomach wall and the small bowel wall and get very, very good looks at the pancreas. In fact, we see it in probably its best definition, and so, we can identify small cysts. We can identify small masses. We can also identify textural changes that really cannot be picked up by other types of imaging devices. And on top of that, then we have the ability to safely biopy. So, if there is a reason to biopsy it, we can safely pass a very small needle under ultrasound guidance into say for a pancreatic cyst or a pancreatic mass and gain tissue and then have a pathologist or a cytologist look at that tissue under a microscope and give us a diagnosis. That has been the workhorse of diagnostics for pancreatic disease. What is exciting about that particular area right now is that we are layering on molecular genetics on top of those biopsies to make decisions about diagnosis, so maybe identifying malignancies before they even show up as a cytologic abnormality, but also another exciting area is using the tissue from a pancreatic biopsy to make unfortunately a diagnosis of pancreatic malignancy but then to go onto the next step and maybe have an input on how that patient should be treated. And if there is a certain type of drug or class of drugs that this patient would benefit as opposed to another patient, so that is a very active area of both kind of clinical involvement as well as clinical research right now, using endoscopic ultrasound and biopsy to acquire tissue, not only just to make the diagnosis but to be involved in what is called precision medicine of this area to try and tailor treatments for individual patients based on their biopsy.

Chagpar That is really exciting, but one of the things that struck me when we started our conversation is that only 15% of patients present early, and then you've got 42.5% who present locally advanced and the other 42.5% who present with metastatic disease. How do you pick up those latter two groups and what is the treatment regimen for

24:26 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0722-Podcast-Farrell_338358_5_v1.mp3 them? Because presumably for early stage pancreatic cancers, you will move along to surgical resection and presumably that will be the mainstay of therapy along with systemic therapy as needed. Is that right?

Farrell That is correct and there has been a lot of advance actually in both our understanding of the treatment and treatment response to pancreatic cancer and why some pancreatic cancers do not respond effectively. There have also

been some advances in terms of treatment regimens over the last 5-10 years, specifically in the area of drugs such as gemcitabine with nab-paclitaxel as well as a regimen called FOLFIRINOX which is now used for pancreatic malignancy, but also I think what people have begun to understand is that, there are probably smaller subgroups of individuals on the order of 2-5% that may benefit from other classes of medications. So, one group that comes to mind are individuals with pancreatic cancer who again have these BRCA mutations and they either have a BRCA mutation because they inherited it or their tumor acquired it over time. And there is a class of drugs called PARP inhibitors that people are studying in this area for individuals with these mutations that also have been tried in other malignancies that have these mutations associated with them. I think one of the hopes and optimisms for the future of pancreatic cancer is that we will identify more of the subgroups of individuals with very specific molecular abnormalities that will allow us to tailor these treatments to these smaller groups rather than the kind of one size fits all. So, in 2018, yes most patients are being treated with combinations of gemcitabine, nab-paclitaxel, FOLFIRINOX for patients who have locally advanced or metastatic disease, but increasingly smaller groups are being targeted with these precision medicine techniques.

Chagpar And so, does the endoscopic ultrasound which allows you to take a closer look at the pancreas, does that also give you a closer look at where this cancer is relative to other structures so that when we think about locally advanced cancer, one that might be unresectable that it gives us some information as to whether this is something that maybe we can resect versus something that we cannot resect?

Farrell Correct. There is one area that we have not really spoken about in terms of how we stage these tumors, it is called borderline resectable disease and these are individuals who have tumors that are involving a portion of a vein or an artery and maybe with treatment over time, a surgeon may be able to resect that, and so that particular group is imaged carefully with a combination of CAT scans and MRIs initially, but often then endoscopic ultrasound comes into play a role to really more closely define how the tumor is affecting a vein such as the superior mesenteric vein or the artery of the portal vein and it really has a very good role in defining that both before treatment and often after chemotherapy and radiation treatment to help really advise and tell a surgeon

27:32 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0722-Podcast-Farrell_338358_5_v1.mp3 what is the likelihood that this tumor has now come off the vein or come off the artery and what is the likelihood that if the patient is brought to the operating room that the tumor could be resected. So, it is beginning to play a resurgent role in that area of staging as well for these patients who are close to being resected but are treated upfront and then ultimately taken to the operating room later on.

Chagpar So, for the vast majority of pancreatic cancer, the mainstay of therapy is some sort of systemic therapy, now in the area of precision medicine with much more targeted therapies, and then you have got this borderline resectable

group which might end up becoming resectable and the early stage ones which are resectable. For the early stage pancreatic cancers, are they treated with systemic therapy upfront as well or are they treated with surgery first?

Farrell Traditionally, the treatment has been such that if a patient is surgically resectable based on a CAT scan or an MRI scan, the patient is taken to the operating room. Increasingly what is happening, and there is an appreciation both from other malignancies such as what goes on and how we treat rectal cancer and also esophageal cancer, there has been an appreciation for the benefit of giving such patients who are clearly resectable treatment upfront and offering them chemotherapy for a period of 3 to maybe 6 months or so and then reassessing them for surgical resection. We think this has biological benefits, it has the benefits of getting the treatment onboard. Sometimes the patient is a little bit hesitant because they hear they have a surgically resectable tumor and they do not want to take any chances, but I think you are going to see more and more data in this area supporting this approach for our treatment of early resectable pancreatic malignancy. Dr. James Farrell is an Associate Professor of Medicine and Digestive Diseases at Yale School of Medicine and the Director of the Yale Center for Pancreatic Diseases. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.