

Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or 1888-234-4YCC. This evening we welcome Dr. Wasif Saif for a conversation about pancreatic cancer. Dr. Saif is an Associate Professor of Medical Oncology and he is Co-Director of the Yale Cancer Center Gastrointestinal Cancers Program.

Chu Why don't we start off by defining what pancreatic cancer is?

Saif I think it is very important for us to first understand what the pancreas is. The pancreas is a pear-shaped organ located deep in the abdomen. The bigger head part is called the head of the pancreas, the part in between is called the body, and the narrow part is called the tail. This is an organ made by nature to produce two kinds of enzymes. One is the enzyme to help with the digestion of food, and secondly to produce hormones such as insulin and glucagon to help us maintain the glucose level. When abnormal cells develop in the part of the gland that produce the enzymes to digest the food, that becomes known as pancreatic adenocarcinoma, or pancreatic cancer, and that is the cancer we refer to when we say pancreatic cancer. When the tumor comes from the part of the pancreas that produces the enzymes such as insulin and glucagon, that tumor is called a neuroendocrine tumor of the pancreas, and it is very important to make a clear distinction between these two subtypes of cancer.

Chu What are the main risk factors that one would typically be concerned about for developing the more common pancreatic cancer?

Saif If you look at the literature historically, the most well known cause of pancreatic cancer is aging, but unfortunately, we are seeing younger and younger patient's every day in our practice. The other risk factors that can lead to the development of pancreatic cancer are smoking and alcohol abuse. Diabetes also has a very interesting relationship to pancreatic cancer. It has shown that chronic diabetes can lead to pancreatic cancer, but the most recent clinical studies have shown that the development of diabetes in a patient without any known risk factors for diabetes can also be a red flag that somebody is developing pancreatic cancer. In addition, patients who also have chronic pancreatitis, or patients with some familial syndromes, can also be developing pancreatic cancer. Patients also can carry pancreatic cancer as a familial problem.

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- Foss How does a patient know that they are developing pancreatic cancer? What are the major symptoms that a patient would experience?
- Saif It's sad to say, but a pancreatic cancer is a cancer which is usually late to be diagnosed, unfortunately, because there are not very clear symptoms that lead to the diagnosis. In general, the most common symptom is jaundice, which means the yellowish discoloration of the eyes and the skin followed by abdominal pain, unexplained weight loss, loss of appetite, and fatigue.
- Foss Are these the same symptoms that the neuroendocrine tumors of the pancreas would manifest or is that a little bit different?
- Saif They are definitely different because there are different chemicals that can be produced by the neuroendocrine part of the pancreas that can lead to different symptoms such as diarrhea, low potassium, hot flashes, cramping in the belly, or shortness of breath, and that is the reason it is so important not only to understand and distinguish between the two entities for diagnosis, but also the treatment and prognosis is different.
- Chu Wasif, as you said, there have been a number of patient's who may not have any symptoms at all, making the diagnosis quite difficult.
- Saif That's exactly true Ed. That's because the pancreas is a very deep-seated organ. As you look at the anatomy, this is an organ that is seated really at the bed of the stomach and then behind is the spine, and unfortunately, no symptoms develop till it is very advanced in stage, and that's the reason the outcome remains very dismal.
- Chu Now for colon cancer we have good screening methods. Obviously for breast cancer and cervical cancer we also have good screening and early detection strategies. Are there any such screening or early detection methods that can be used to try to catch pancreas cancer in an earlier stage?
- Saif Unfortunately, there is no standard screening test available as of today. The main thing is that a high degree of suspicion should be developed in a patient who develops any of those symptoms. The test called CA19-9 that we use clinically in patients who have pancreatic cancer has been tested in the screening mode and was not found to be successful in detecting pancreatic cancer. So, right now, unfortunately, other than being very cautious, knowing the prior family history of the patient, and any unexplained weight loss or development of jaundice, seeking medical advice immediately is the only tool right now to detect it at an early stage.

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- Foss If a patient is receiving an annual physical, is it likely that this would be picked up?
- Saif Only if somebody has abnormal liver functions. If somebody who has liver enzymes is checked for a reason, either they are on a cholesterol lowering medication or some other reason, and they find that the patient has abnormal bilirubin, which means they are jaundiced or they have a high level of liver enzymes, that may be one way to look further into the reason for liver enzyme elevation and can detect pancreatic cancer at an early stage.
- Foss Patients talk about pain with advanced pancreatic cancer, and that's one of the major problems that a patient experiences. Is it likely that a patient would actually present with pain?
- Saif Pain is one of the most common symptoms and the most devastating problem for the patient, family, and the physician. Pain, definitely unexplained pain, and particularly when the pain is accompanied by weight loss, is a very concerning reason to look into the etiology, such as pancreatic cancer.
- Chu Typically, what kinds of tests would than need to be done to further define what is going on with the patient?
- Saif First of all, the rule of thumb is that we do a CAT scan of the abdomen and pelvis with and without a CT scan of the chest. That is the best test to look for a mass in the pancreas. After we see a mass, the next step is to get a tissue diagnosis, and the best way that we are doing that at Yale Cancer Center is to perform an endoscopic ultrasound biopsy, where a specialized gastroenterologist pass an endoscope through with a small needle at the tip of it and go into the intestine and get a biopsy of the tissue. At the same time, as I mentioned earlier, a bulk of these patients also develop jaundice at the time of presentation. Sometimes we use another method called ERCP, where the patient has another scope pass through the intestine, and we not only get a tissue sample for the diagnosis, but we also place a stent to open the bile duct, which is narrowed down by the pancreatic cancer leading to jaundice.
- Foss Are these tests pretty specific? In other words, is it likely that a patient could have pancreatic cancer and these tests wouldn't show it?
- Saif Very rarely. These tests have pretty high sensitivity and specificity in terms of diagnosis, so after we have high suspicion, and after we follow those tests, in nearly every case we are able to procure and secure the diagnosis.
- Chu When patients undergo these tests, because its sounds kind of complicated, is there any pain

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involved? Does the patient experience any discomfort when the gastroenterologists are doing these procedures?

Saif Ed, the point that patients and their families have to realize is that these tests have to be done in a specialized center where people are specialized and trained in this field, and luckily, at Yale Cancer Center, we have a multidisciplinary team of people from all fields, including gastroenterology, endoscopic serology, pathology, medical oncology, surgical oncology, radiation oncology, and many more, who are a part of this fund, and are devoted to help these patients. That's the reason we rarely see any problems dealing with these procedures to confirm the diagnosis.

Foss Supreme Court Justice, Ruth Bader Ginsburg, was recently diagnosed with pancreatic cancer. I understand that she was diagnosed at an early stage disease. Can you tell us a little bit about how it was detected so early and how her case may be typical or unusual for other patients?

Saif She was a very lucky and fortunate lady and I am very happy for her. I think the reason that happened, as you may learn from the news, is that she has a history of colorectal cancer, which was treated at the National Cancer Institute between 1999 and 2000, and as a follow-up for that tumor, she was found to have a mass in the middle part of the pancreas that was around 1 cm, and finally she was able to go for surgical resection. Luckily she was diagnosed at an early stage, which has a better outcome, and as we all know surgery is the only potential cure for pancreatic cancer. But as I mentioned earlier, we do not do CAT scanning in other patients on an annual physical, so it is very hard to do the same thing in the mass population without knowing the benefit of CAT scan and doing it in a mass population among our patients.

Chu Wasif, now that she has had her surgery, it sounds like she has recovered so well that she is actually back at the Supreme Court. Should she be receiving any follow-up therapy such as chemotherapy or radiation therapy?

Saif That is a very important question, but I'd like to make it a little more generalized. When we see a patient who undergoes surgical resection we look at many factors. Of course, we look at the staging, and also we look at some histological factors. Histological factors for the patient means the factors, the features, that we see under the microscope that tell us about the aggressiveness of the tumor, such as if the tumor is trying to go around the nerves, if the tumor is trying to enter the blood vessels, how many lymph glands were positive in that tumor, and finally, if the margins were negative. Looking at those things, we have two ways of treating these patients. The most common mode that people are using in United States is

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to combine chemotherapy with radiation therapy. However, there is emerging clinical data that supports that using chemotherapy alone can also give you a similar benefit. So, in most populations where we see surgical resection being done, we know that something needs to be done to prevent this cancer from coming back, and that is why we recommend chemotherapy or chemoradiotherapy based on the features we find on the final diagnosis.

Foss You mentioned that Justice Bader had pre-existing colon cancer. I am wondering, is there an association between other GI cancers and pancreatic cancer?

Saif That's an excellent question Francine. As you know, HNPCC, Hereditary Nonpolyposis Colorectal Cancer, is a risk factor for patients to develop pancreatic cancer and colon cancer. Lynch II syndrome is another syndrome where patients can develop colon cancer and pancreatic cancer. Peutz-Jeghers syndrome is another syndrome. So, there are a lot of familiar and inherited conditions that can lead to multiple gastrointestinal cancers and that's the reason high vigilance and prior history knowledge is very important in determining the diagnosis for these patients.

Foss If a patient has a family history of one of those diseases, should they be asking their doctor for a genetic test, and if so, what kind of test?

Saif That's a very big question; let's define it a little bit in different portions. The first part is that there is a familial pancreatic cancer. Patients can run pancreatic cancer in their families, and we are still trying to learn about the genetic makeup of those families. Second are the syndromes which carry the risk of pancreatic cancer, such as the one we discussed earlier, and many others such as ataxia, telangiectasia syndrome, FAMMM syndrome, which is Familial Atypical Multiple Mole Melanoma syndrome where the patient can develop melanoma and also pancreatic cancer, and many others. There is no question that we need to really understand the family history of those patients, but at the same time, we are also trying to learn about the relationship between pancreatic cancer and many other common cancers, such as breast cancer and ovarian cancer.

Chu Is there a familial syndrome in which if there are mutations, such as BRCA1 and BRCA2 genes, that patients would be at an increased risk for developing pancreatic cancer?

Saif As you know, there are two breast cancer genes, BRCA1 and BRCA2. A patient with BRCA1 and BRCA2 not only has an increased risk of developing breast cancer and ovarian cancer, but also has an increased risk of developing pancreatic cancer. We at Yale Cancer Center, as a multidisciplinary team, are working on this front and we are following patients

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with these syndromes. We have developed our own institutional based screening program for those patients with high risk, or with these positive mutations in their families.

Chu Maybe to help put things into perspective Wasif, out of say 100 patients that you see with pancreatic cancer, how many have what we would consider to be a familial or genetic component as a cause for that cancer?

Saif Right now I would say at least 10% to 15% of those patients do have a familial or inherited component that we are able to identify.

Foss Can you talk a little bit about age? We didn't get into this in detail, but my understanding is that most pancreatic cancer occurs in mid- life and I am wondering what the incidence is in younger people versus older people, and what the peak incidence for the disease is?

Saif If you look historically, we used to read that pancreatic cancer is a seventh decade disease, and I wish that could be the case. Of course the bulk of patients we see in our practice are within that, but unfortunately, currently, I am dealing with eleven patient's who are between 30 to 45 years of age, which is very disturbing. That's the reason it is very important for us to learn about the genetic makeup of these patients.

Foss Thank you very much Wasif. We would like to get into treatment in a little bit more detail when we come back, but right now we need to take a break. You are listening to Yale Cancer Center Answers, and we are here discussing the treatment of pancreatic cancer with Dr. Wasif Saif.

Medical Minute

Here in Connecticut the American Cancer Society estimates that almost a thousand people will be diagnosed with colorectal cancer every month. The good news is that when detected early colorectal cancer is easily treated and highly curable. That means that if you are over the age of 50 you should have regular colonoscopies to screen for this disease. In the case of patients that develop colorectal cancer, there are more options than ever before thanks to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for colorectal cancer. Patients enrolled in these trails are given access to medicines not yet approved by the Food and Drug Administration. 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.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by

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co-host Dr. Ed Chu and Dr. Wasif Saif, a medical oncologist at Yale Cancer Center. Wasif, we talked a lot about the diagnosis of pancreatic cancer and some of the treatment approaches, but could you take us through this from the time the patient say is diagnosed with advanced pancreatic cancer; we talked about the different tests and x-rays the patient would have, but when the patient is ready to move on to treatment. Can you talk a little bit about chemotherapy and the role of radiation therapy in this disease?

Saif The way we approach these patients is we have a multidisciplinary approach. Most of these patients are discussed at a Gastrointestinal Tumor Board where we have our experts like Dr. Ronald Salem, surgeons, radiation oncologists, Dr. Jonathan Knisely, Dr. Kenneth Roberts, and Dr. Bryan Chang, as well as our radiologists who are a part of that team. We discuss the case and make the final decision for the patient on whether this patient is surgically resectable at that time, or if the patient will be able to go for surgical treatment. If the patient is not surgically treatable at this time, we define the patient into two other groups. The first group is borderline resectable, which means that we think that if we have some benefit from the chemotherapy and/or the radiotherapy, this patient may be able to go for surgical resection. The second group is the patient where we see the CAT scan and we believe that, based on the findings, this patient will not be amenable to surgical resection. The biggest group that we see, unfortunately, is the patients with stage IV pancreatic cancer where the tumor has already advanced to the liver. So, based on those factors, we then decide whether surgery, chemotherapy, or chemoradiotherapy is the best option for the patient.

Chu In general, when a patient comes to you with let's say stage IV metastatic pancreatic cancer, surgery and radiation therapy are usually not a consideration, is that right?

Saif Correct. When a patient has stage IV cancer, in that case, chemotherapy is the way to move forward. That's really the key to understanding that we have a lot of clinical trials that we are developing to improve the outcome for those patients.

Foss We have heard a lot in some of our previous shows about these new-targeted agents out there for cancer. Can you talk a little bit about pancreatic cancer and whether any of this targeted therapy is specifically applied?

Saif The story about pancreatic cancer had been quite challenging until today. There had been two antibodies which have been approved by FDA for use in colon cancer, one is called bevacizumab, which is an anti-vascular endothelial growth factor antibody, and the second called Erbitux, or cetuximab, which is an anti-epidermal growth factor receptor antibody. Both of these antibodies were tested in pancreatic cancer and were found not to be of any

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benefit when added to gemcitabine. But luckily, in the last few years, one targeted agent has shown benefit, it is called Tarceva, or erlotinib, and is a small molecule, an oral medication, which acts against the same target epidermal growth factor receptor. When this drug was combined with Gemzar, a survival benefit in these patients was shown.

Foss Would you be using chemotherapy in all patients, and then adding these biological agents, or sometimes would you just use the oral biological agents?

Saif We definitely know the drug that has to be given at this time, also the clinical trial has to be gemcitabine and we also like to enroll patients in a clinical study because we believe that this is just the beginning of our fight against pancreatic cancer. Even having those drugs available, we still don't have the best outcome for those patients. However, if the patient declines, or does not qualify for a clinical study, in those cases we can use Tarceva with gemcitabine.

Chu Wasif, you are one of the leaders in the field throughout the country in trying to develop new agents, new treatment strategies, for this disease. Can you tell us a little bit about some of the very interesting clinical trials that you have been conducting at Yale Cancer Center?

Saif As you know, we recently completed a clinical trial with the drug called Genexol-PM, which is a special kind of taxane. Recently we did two clinical studies, and we still have patients on the treatment with the drug called PHY906. As you know, PHY906 is a very interesting drug. It's a combination of Chinese herbs, which have been shown to not only decrease the side effects of chemotherapy, but also to increase the cell killing activity of the chemotherapy. We did that clinical trial and we are still having patients see the benefit from those drugs. In addition to that one, we are opening a clinical study in a week's time where we are using a drug called S1. S1 is an oral chemotherapy that has already been approved in Japan for many GI tumors, and now it has been brought to the U.S. for further development. We will be using this drug with gemcitabine in the first line treatment of pancreatic cancer. In addition to that one, we are also using a new agent called MK. This is a drug that affects an enzyme called Aurora-A kinase inhibitor. In simple words, all the cells have to divide, and before division, the nucleus divides and then they develop spindles that attach to two sides of the nucleus. This is the enzyme that initiates the division of the cell and this new target we will be testing soon in these patients will be the one that will affect that target and inhibit the cell division. Right now the field is open and we are very excited about all the clinical studies that we are working on and the ones in the pipeline.

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- Foss Are these studies open only for patients that have failed conventional therapies, or is it possible for a patient to get into a study when they are first diagnosed?
- Saif As I mentioned earlier, the gemcitabine and S1 studies are for patients that are newly diagnosed with pancreatic cancer, and we are looking for patients that are chemo-naïve; in simple English, patients who were just diagnosed and never received any chemotherapy for their stage IV or stage III pancreatic cancer. The other studies I have mentioned are for patients who have already received gemcitabine and now they are looking for other treatment options for pancreatic cancer.
- Chu Sometimes people who are listening might feel a little weary when they hear this idea of a clinical trial. Wasif, maybe you can reassure patients who are hearing about all these different trials that you are offering them, and that they really are important and hopefully can provide some benefit for them?
- Saif I will describe it in three forms. First of all, there is the cancer treatment. We know this is a very deadly tumor, so definitely there is no blind study. Patients always ask me, “Will I be getting the chemotherapy?” The answer to that is yes, everybody will be getting the chemotherapy. Number two, this is a joint fight against pancreatic cancer. When you are on a clinical study, not only are you trying to add another thing to the menu for your treatment, but I also believe that you are helping humanity. If the drug works out, tomorrow you will be a part of the blessing to humanity. Thirdly, when you are on a clinical study, not only are you going to be seeing me and my team, but the research nurse will be chasing you like a hawk. I believe that in a way, looking at the studies NCI has done in the last few years, we know that patients on a clinical trial seem to do better, and seem to live longer, partly because they have better communication with the team that is taking care of them. There is no question that I assure my patients and their families that any treatment we are offering has a rationale scientifically, and the ideology is to help these patients live better and live longer.
- Foss That brings up a really important point Wasif, that we all think about with cancer, and that is quality of life. We talk a lot about treatment, but quality of life is as equally important for many patients. One of the advantages recently, is that a number of drugs are now available orally, and that certainly improves quality of life for patients in terms of running back and forth to see the doctor, but can you talk overall about quality of life issues as a patient moves forward with treatment for pancreatic cancer, and what kind of support is out there for patients in a community setting?
- Saif Francine, you are dealing with the most important aspect of pancreatic cancer that sometimes some physicians forget. Pancreatic cancer is a classic example of a tumor where we have to

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have supportive care involved. When I see these patients, I always tell them that supportive care is more important, or as important, as dealing with cancer. I always use my quotation, "I don't treat cancer, I treat patients," and we have a team involved with patient care; we have a nutritionist, a social worker, a case manager, and we have palliative medicine folks who work with me very closely to help these patients. As you also know, we have been developing a lot of studies and a lot of publications to help patients with awareness of the use of pancreatic enzymes, and about awareness of the importance of nutrition in these patients. It is the key element, because these are patients where not only is the cancer very challenging, but at the same time it is challenging in terms of the physical and mental situation of the folks. As you may know, recently we had one of the biggest articles published on the role of depression in pancreatic cancer and how important it is to deal with that problem from day one of the diagnosis of these patients. Also, we found that there is a chemical relationship between depression and pancreatic cancer. To sum up, we have a team and this is the most important target that I deal with when I see patients from day one. We offer all the services to them and we keep asking them, and whenever see a necessity, we try to involve those folks in the care of those patients.

Chu Wasif, can you say a little bit more about the nutrition aspect, because I know you focus a great deal on trying to make sure upfront that the nutritional status is always maintained. Why is nutrition such a major element, especially in patients with pancreatic cancer?

Saif I think this is explained by what I started my discussion with today, that pancreatic tissue has two main important functions. The first important function is that this is the biggest gland in the body that produces enzymes to digest food. As you know, there are three kinds of foods that we eat; starch, carbohydrates, fats and also the proteins. These three kinds of food that we eat, and these three enzymes, are produced by the pancreas. So, when somebody develops pancreatic cancer, either the amount of enzymes produced by the pancreas is decreased, or the kind of enzyme produced by the pancreatic cancer is not the normal enzyme; it's either a heavy weight or lower weight, or an abnormal chemical composition that does not help us to digest food and people develop malabsorption. In addition to that, the cancer itself also produces a chemical called cachexin that leads to cachexia, which in simple English means it leads to lack of appetite and weight loss. Keeping those things together may become very challenging. These patients have pain also, they are taking pain medications, they have constipation, nausea, and because of that they don't feel like eating anything and it becomes very important that we work on nutrition. To start with nutrition, we have supplied them with the replenishment of pancreatic enzymes. We also have found that those enzymes work better if we give them medication to decrease the acid production in the stomach, and by giving that medication the enzymes work better and then, if the patient cannot eat by mouth, we have to look for other routes for administration of food, either by

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placing a feeding tube in the intestine or the stomach or by giving food through the vein for a certain time.

Foss Wasif, is there is a specific support group or a national organization for pancreatic cancer? How can a patient get more information about these clinical trials?

Saif At Yale Cancer Center patients can either call us or they can go to yalecancercenter.org. That's the best way to approach us, and we are always willing 24/7 to answer people's questions and help them out. The second way is that there are multiple NGO's and non-governmental organizations such as pancan.org and may other pancreatic cancer awareness groups. There are a lot of national organizations that are supporting patients and their families and I am trying to be a part of most of them, so patients can always find us either through Yale Cancer Center website, or through those centers, and we will be happy to help them out.

Chu You have been listening to Yale Cancer Center Answers. We would like to thank our guest Dr. Wasif Saif for joining us this evening. Wasif, again thanks very much for being with us.

Saif It's my pleasure Ed.

Chu We look forward to having you on a future show. Until next time, I am Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

If you have questions or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past program. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.