Dr. Wasif Saif, Managing Pancreatic Cancer February 14, 2010Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation you can contact the doctors directly. The address is canceranswers@yale.edu andthe phone number is 1888-234-4YCC. This evening Ed welcomes Dr. Wasif Saif. Dr. Saif is an Associate Professor of Medical Oncology at Yale Cancer Center and an expert in the treatment and research of pancreatic cancer.Chu Can you start off by defining for us what pancreatic cancer is?Saif As you know, the pancreas is a big gland sitting in our body. It is a pear-shaped gland, which is lying on the side. The bigger part, or bigger end of this gland, is called the head, followed by the neck and the narrow part is called the tail. There are two functions of the pancreas, one is to produce enzymes to digest foods and that part of the gland is called exocrine and when we talk about pancreatic cancer, we talk about the cancer cells which originate from the exocrine part of the pancreas. It is also very important to remember that the second most important function of the pancreas is to produce insulin and glucagon that helps us to maintain our glucose level. When the tumor cells originate in those cells then we will call it endocrine tumor of the pancreas.Chu Obviously from your description, the pancreas really is a very important organ and if cancer involves the pancreas, it could result in some pretty significant disorders.Saif That's exactly true. As I mentioned, not only can it lead to malabsorption, cachexia, which is defined in simple terms as weight loss, lack of appetite, and lack of energy, but also it can lead to brittle diabetes, which in simple English means that if people are diabetic already, their diabetes control could be very difficult to manage, or for people who are not diabetic, they can become diabetic after developing pancreatic cancer.Chu How common is the disease, and in what age group do we typically see pancreatic cancer?Saif The sad news Ed is that despite all the research we have done over so many years, the incidence of pancreatic cancer is growing tremendously; the statistics from 2009 show that 42,470 patients were diagnosed with pancreatic cancer in this country, and unfortunately we lost about 35,760 patients. That really tells us the incidence, despite all the progress in research, is going up. The most common textbook answer for this is patients are known to develop this cancer in their 70s, but that's not very common unfortunately, we are seeing this in younger and younger patients. I would say the bulk of patients we see in the practice are 50 to 70 years of age, but also we are seeing many young patients developing this deadly disease.3:04 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3Chu Do we know why we are seeing this disease present in younger patients?Saif I would say there could be multiple factors. One thing is that now we have better designs of testing to diagnose this disease properly then just diagnosing somebody with an unknown cancer. At the same time, I think genetic variations, genetic mutations, and genetic abnormalities must be playing a role in developing cancer in these patients in an early stage

and I think that will be a very important topic as we move forward in the research for pancreatic cancer.Chu You just touched on this issue of the genetic makeup, what do we know about the genetic basis for pancreatic cancer, is this disease inherited?Saif I think that's pretty true, Ed. Actually, if we look at the medical sciences, pancreatic cancer provides one of the best models when it comes to understanding the molecular basis of cancer, but unfortunately, we are still not able to really catch those targets to treat this cancer well, but in simple words, they are different syndromes which are affiliated or associated with the development of pancreatic cancer. One of the most important, of course, is a familial pancreatic syndrome, where the patient has pancreatic cancer in the family. But the second most common syndrome we see is the Lynch II syndrome, or so called HNPCC, where patients develop many cancers including pancreas and colon before the age of 50.Chu There is also an association between mutations in some of the breast cancer genes and pancreatic cancers, is that correct?Saif That's exactly true, there are two genes, breast cancer gene 1 and breast cancer gene 2, and there is currently a lot of research going on at Yale Cancer Center with folks in the pathology and the genetic department because patients who carry that gene not only can develop pancreatic cancer, but can also develop breast cancer and ovarian cancer. Recently we published data on our patients where we found that certain chemotherapies could be more beneficial to give to these patients compared to the conventional chemotherapy.Chu In addition to the genetics of pancreatic cancer, what do we know about the other risk factors for developing pancreatic cancer?Saif In addition to the genetic factors, one more important thing I would like to mention is the FAMMM syndrome, or so called familial atypical mole-melanoma syndrome. But in addition to that one, there are other risk factors that can lead to the development of pancreatic cancer. We should not forget smoking. Smoking is a very important risk factor for pancreatic cancer, as well as alcohol abuse, patients with chronic diabetes, or patients who5:34 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3develop diabetes de novo without any risk factors, or patient with chronic pancreatitis. In addition, there are many other risk factors which still need to be studied. But overall, we always say that this cancer definitely has some environmental as well as genetic factors playing together in the development of cancer.Chu It's interesting, we always associate smoking with the development of lung cancer, but as you just mentioned, there is an increased risk for individuals who smoke to develop pancreatic cancer, do we know why smoking can increase the risk?Saif I think one thing is that if you look at the literature, the epidemiological studies show that about 30% of cases who have pancreatic cancer have a history of severe smoking, and as you know, smoking contains tar and many other oxygen radicals that can lead to cancer. Interestingly, a study was published a few years ago that showed that people who have very bad dental caries due to smoking likely also show a risk factor for developing pancreatic cancer. We are also learning there are some drugs that work in pancreatic cancer such as erlotinib, or Tarceva. There could be the possibility that patients who are smokers, or

nonsmokers, may also lead to response or no response to those drugs. I think this is really a Pandora box that needs to be studied again compared to the historical association with lung cancer only.Chu A few years ago there was a lot of publicity surrounding the potential association between coffee use, coffee abuse, and pancreatic cancer, what are your thoughts, what is the latest on that?Saif That's a very interesting question Ed. As you know, in 1994, studies came out that really scared everybody into thinking that coffee can lead to pancreatic cancer, but followed by that, there was a meta-analysis published by Japanese investigators that showed that a small amount of coffee may actually be protective compared to a large amount of coffee maybe causing some risk. I think it is very important to understand that the amount of coffee we take in, in the United States, could be almost like a jug compared to coffee taken in, in Japan or China. If you go to China and you buy coffee mugs, the coffee mugs are almost the size of your half thumb. I think that's very important and I think excess of anything is bad, like alcohol excess is bad. Similarly, I think coffee has some controversial risk of developing pancreatic cancer, but so far nothing can be said for sure that it is the cause of cancer.Chu Wasif, lets go back and review the typical symptoms that an individual might have if in fact they have an underlying pancreatic cancer.Saif The most common symptoms are very nonspecific. The patient can develop pain, jaundice,8:06 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3which is defined as yellowish discoloration of their skin or their eyes, and they can also develop weight loss. These are the three classic symptoms that we see in patients, but in addition to those, one may see other symptoms develop. The patient can also develop clots, or a DVT, without any known reason because this cancer makes the blood very hypercoagulable and leads to clotting and it has also been shown in clinical trials that these patients can develop depression. A study was done in VA Hospitals about ten years ago that showed that an unknown reason for depression could be pancreatic cancer. I think the unfortunate message is that the cancer gives very nonspecific symptoms that can be confused with many other illnesses.Chu Are there any screening methods that are currently available to help identify which patients might have pancreatic cancer?Saif There is no approved clinic method available. There is a marker called CA 19-9, a so called carbohydrate antigen 19-9, and it is a blood test, but unfortunately that testing of blood did not show any clear evidence or development of cancer. However, at this time just having a very high clinical vigilance is important, and also having an understanding of your family history and the development of symptoms which cannot be explained. For example, if somebody starts losing weight without any intention to lose weight, or if somebody who is lean, skinny, and does exercise very regularly and has no family who has diabetes, if those patients develop diabetes, I think these are the signals that you need to seek medical attention.Chu So there are no noninvasive imaging tests like CAT scan, ultrasound, or MRI that could help to identify it?Saif No prospective studies have been done so far; however, in certain cases we do perform endoscopic ultrasound where a gastroenterologist at Yale Cancer Center performs an endoscopy along with

the ultrasound probe and tries to look at those areas. But mostly, we do those procedures in high-risk patients or when we have any clinical suspicion that somebody will be developing a pancreatic cancer. However, these tests have not been tested or approved by the FDA to be used on a mass basis to screen patients for pancreatic cancer.Chu Wasif, if an individual presents with some of the symptoms that you just described, what should they do, who should they seek out medical attention from?Saif I think the first person they should go to is of course their primary doctor, or ask to be seen by a gastroenterologist. They need to really look at the patient, examine the patient, and if they need to have an endoscopy done, or if there are jaundiced and need a stent to be placed,10:41 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3then a procedure called ERCP can be done and from there, after the diagnosis has been performed, then they are referred to see a medical oncologist and a surgical oncologist. After the evaluation by a medical oncologist and a surgical oncologist, then we will decide whether the patient needs to see a radiation oncologist. I think in simple words, it is a multidisciplinary approach to treat these patients to give the best to them. However, it has to start from the first drop of rain that could be their primary doctor, or that could be their gastroenterologist.Chu Typically the diagnosis of pancreatic cancer is made by biopsying a suspicious-looking mass?Saif Yes exactly, as we always say in cancer we need tissue. Similarly, in pancreatic cancer, we need a tissue diagnosis to move forward not only to confirm cancer, but as I mentioned, it can be different types. It could be exocrine or endocrine, and not only are the treatments different, but the prognoses are different as well. Therefore, it is very important to have a tissue diagnosis. In most cases, the diagnosis is performed by the endoscopic ultrasound, as I mentioned earlier, which is done by a gastroenterologist. However, in cases where we see a mass in the liver, or where the tumor in the pancreas is not easy to approach using the endoscope, then sometimes we end up performing a CT-guidance biopsy, or an ultrasound-guided biopsy, by a radiologist specialist called an interventional radiologist.Chu In most patients, unfortunately, when they present to say us, the medical oncologist, the disease is typically at a more advanced stage, say compared to patients with early stage breast cancer or colorectal cancer. Why is that, why do these patients typically present at a much more advanced stage?Saif As I mentioned to you, this is a tumor that causes symptoms that mimic many other common illnesses. If somebody has abdominal pain, they may blame it on some maldigestion; they may blame it on an ulcer. At the same time, the pancreas sits deep seated in the belly and unfortunately the symptoms don't really become visible till the tumor has really spread into distant parts of the body, and we do not have any screening tools available to screen for this disease early. I think that's one of the unfortunate reasons that this cancer, when it comes to our attention, is being diagnosed at a very late stage.Chu I guess one of the take-home messages for our listeners would be that if they should have the new onset of symptoms that are unusual and that persist for more than just say a few days, they really should seek out medical attention and not just assume that it's nothing serious.13:16 into

mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3Saif I think you are exactly right Ed, prevention is always better than treatment. At the same time, the bottom line is that we need to be like a good police officer. We need to develop a high degree of suspicion, particularly in circumstances where we cannot attribute our symptoms to something very simple.Chu I think that's obviously really good advice for our listeners out there. We are going to take a short break for a medical minute. Please stay tuned to learn more information about the treatment and evaluation of patients with pancreatic cancer with our guest expert this evening Dr. Wasif Saif from Yale Cancer Center.Chu Welcome back to Yale Cancer Center Answers. This is Dr. Ed Chu and I am joined here in the studio this evening by my good friend and colleague Dr. Wasif Saif from Yale Cancer Center to discuss the diagnosis and treatment of pancreatic cancer. Before the break, we were talking about how patients with pancreatic cancer will present, and how it's diagnosed. At the beginning of the show we actually talked a little bit about the different kinds of pancreatic cancer, its not just one particular type, can you review for us the different types of pancreatic cancer that you typically see in your clinic?Saif Typically if we see 100 cases about 95% of those cases are exocrine pancreatic cancer, which is the notorious pancreatic cancer we talk about. Those are the patients where the tumor cells are originating from the ductal glands of the body of the pancreas. In addition to that, about 5% of those 100 cases are the ones we see with neuroendocrine, or endocrine tumor of the pancreas, where the cells originate from those cells in the part of the gland that produces insulin, glucagon, or other transmitters like that. When we talk about exocrine tumor of the pancreas, it is also very important to know that the most common, 90% of cases, are adenocarcinoma; however, there are some variance of that tumor. There is acinar cell carcinoma, mucinous carcinoma, but most interestingly, we are now developing new technologies and our pathologists are getting smarter and smarter and giving us better16:06 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3information. Now we talk about some borderline cancers, such as IPMN, intrapapillary mucinous carcinoma. Definitely, as I mentioned earlier, it is a multidisciplinary modality treatment for this cancer and the involvement of every modality is crucial in the development of the best treatment modalities for these patients.Chu We will get to that in a moment, but can you help put this disease into context for our listeners out there? Over the last three to four years, its remarkable how may famous celebrities and sport stars have developed pancreatic cancer. To put this in the appropriate context, Patrick Swayze.Saif Correct.Chu What type of pancreatic cancer did he have?Saif He had the exocrine pancreatic cancer, which I told you is the most common cancer of the gland. He had that kind of cancer and there was a great news article in the New York Times that said when Patrick unfortunately developed pancreatic cancer, they thought maybe more attention would be given to the treatment of pancreatic cancer, and I think that really goes to the historical name for pancreatic cancer, 'the orphanage tumor'. Up until 2000, there was no special funding available from NCI even for this cancer. It was up

until 2000, when the NCI formed the task force to develop better treatment options for pancreatic cancer.Chu Steve Jobs also is also widely known to have pancreatic cancer, but as I understand he has a different pancreatic cancer than Patrick Swayze?Saif That is true Ed, he has the 5% kind of cancer so the endocrine tumor of the pancreas, and in general, patients who have that form of cancer have a much better prognosis compared to patients who have exocrine tumor of the pancreas.Chu Patrick Swayze, unfortunately, once his diagnosis was made he did not live that much longer, where Steve Jobs actually has done quite well with his disease.Saif That's exactly true, and I think that goes back to the basic point that proper diagnosis is such a crucial thing in determining the treatment as well as the prognosis for these patients.Chu You mentioned a moment ago the multidisciplinary approach to taking care of patients with pancreatic cancer. Describe for us the multidisciplinary team that you have at Yale Cancer Center when you are evaluating a patient with pancreatic cancer.18:28 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3Saif We are very blessed that we have one of the key team leaders known for their work nationally and internationally. I run the Medical Oncology Program for pancreatic cancer, and at the same time my colleague, Dr. Ronald Salem, is the Surgical Oncologist and Professor of Surgery. In addition we have a GI team including Dr. Harry Aslanian, Dr. Uzma Siddiqui, and Dr. Priya Jamidar. We have radiation oncologists, Dr. Jonathan Knisely, and Dr. Bryan Chang. We have genetic testing doctors, Dr. Ellen Matloff. We also have a radiologist who works with us very closely. This is like teamwork and we work together to help use make the correct and a quick diagnosis for the patient, but also provide the patient the best possible treatment for them so that they can achieve the best outcome available at this time in any state-of-the-art cancer center on this earth.Chu Very broadly, what are the different treatment options available to a patient with this disease?Saif In simple words the treatment options can be divided into three groups. One is surgical resection, or surgery. The second is chemotherapy. Chemotherapy is again divided into two groups, one is the cytotoxic chemotherapy, or the general form of chemotherapy, and the second form is called targeted agents. These are the agents that target a specific target in the pathway of cancer and try to attack the cancer. And the third treatment is radiation therapy, where we give x-rays to palliate or shrink the tumor.Chu I imagine surgeries are typically reserved for those patients who have disease that's very locally confined to the pancreas.Saif That's true. Surgery is confined mostly to the patient where the tumor can be surgically resected or where after giving chemotherapy or with radiation therapy, the tumor has shrunk down enough that we can take the tumor out. However, sometimes we offer surgery to patients to palliate their symptoms. For example, if somebody develops obstruction of the small intestine, then in those cases we have to bypass that obstruction through surgery. Surgery is confined and divided into two groups; one is curative surgery and the second is palliative surgery.Chu When would you typically recommend the use of radiation therapy?Saif The role of radiation therapy is becoming more and more interesting and controversial in the treatment of

pancreatic cancer. Overall, the most common patient to receive radiation therapy are those who have locally advanced pancreatic cancer. These are the patients where the tumor cannot be resected out and trying to invade the surrounding blood vessels. The second most common patients are the ones who have gone for surgical resection of the pancreas, but unfortunately under the microscope we still see few cancer cells present at the21:03 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3 margins of the tumor area taken out by the surgeon, or in the third case we give radiation therapy to patients who have pain. For example, pain in the pancreas is not controlled by pain medications, or unfortunately if somebody develops disease in the bone or other parts of the body. It's given to some patients for curative intent, if they have cells left after surgery, secondly for patients who have locally advanced disease, and thirdly for palliation of symptoms in stage IV disease.Chu Wasif, as you know, the big buzz over the past few years in cancer therapy in general has been the use of so called targeted therapies, and as you mentioned, one of the breakthroughs for the treatment of pancreatic cancer has been the development of a targeted therapy. Can you review with us what targeted therapy is now being used to treat pancreas cancer?Saif Ed, as you know, the efforts have really tripled, I would say even beyond that over the last few years to improve outcomes for these patients. Multiple drugs were tested, but unfortunately so far only one drug has shown benefit, and it's called erlotinib, or Tarceva. Tarceva is a chemotherapy drug which is given in the form of a pill and it is given in addition to standard chemotherapy called Gemzar, or gemcitabine. This targeted agent basically is called a tyrosine kinase inhibitor. This is a drug that is taken by mouth, goes to the tumor level, and tries to inhibit the growth factor that helps the tumor to grow. So far this drug, when tested in combination with Gemzar, shows a statistical benefit; about 30% overall survival benefit compared to patients who did not get this drug and this is really at least a step forward in the treatment of pancreatic cancer.Chu One of the nice things about this drug is that it can be taken orally.Saif Exactly, convenience is definitely a major part for these patients; however, it is also important to keep in mind that these patients do have some GI symptoms. Definitely it is very important for us as physicians to select the right patient for the right mode of therapy.Chu Wasif, you are clearly one of the leaders in this country and really worldwide in trying to develop new treatments for pancreatic cancer. Can you tell us a little bit about the type of clinical research that you are currently conducting at Yale Cancer Center? Saif We recently finished three interesting clinical trials. We just published a drug that we call Genexol-PM, which is a special kind of Taxol, which does not carry a special chemical called cremophor, which leads to the hypersensitivity reaction with these drugs.In addition to that one, we recently published another study with a drug called LY, which is a leukotriene receptor antagonist. As you know in asthma and in other some inflammatory diseases some chemicals are produced, and we found that those chemicals also play a role in cancer23:51 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3 development. But the most interesting

part that we have done recently, and just published a very interesting paper on is an herbal medication called PHY906. Since I came to Yale and we found this drug was here a few years ago, we got very interested and became intrigued by the data presented to us by our senior colleague Dr. Tommy Chang. Based on the pre-clinical data, we did a clinical trial and we are very pleased to say that we are almost done with the first part of the study in pancreatic cancer that looks very exiting. Not only did we find that we were able to give a very high dose of chemotherapy without any additional side effects, but overall the quality of life has very much improved in these patients. I think that's just the beginning, we are working on two more drugs. Currently we are working on a drug called MK-5108 that is a new drug also given by mouth which is very convenient, and is going to stop the enzyme that starts the cell division. We are now looking at another drug called NV-196, which is basically a flower bean-like drug that will also help to overcome the resistance caused by the cancer cells towards the standard chemotherapy in pancreatic cancer.Chu If listeners out there are interested in learning more about any of these drugs and the clinical trials that you are involved with, how can they get that information?Saif Ed, the world has become very small with the use of the internet and web, but I think they definitely should call Yale Cancer Center or log onto Yale Cancer Center's website, or call my office and my research nurse, because we definitely want to have these people. Keep in mind that we have invested our lives to help these patients and we are always willing and available to these patients to improve their outcome and give them the hope that they are looking for.Chu I would just note to listeners out there, they can go to yalecancercenter.org and then click on the GI disease program and they will actually find a listing of all the clinical studies that Dr. Saif and his team are actively involved in. Wasif, you are I know a very big supporter, a big proponent of the supportive care aspects for patients with pancreatic cancer, and as you have described already, patients with this disease really do have special issues that need to be addressed. Talk to us a little bit about the role of supportive care in the treatment of these patients.Saif I have a very famous quotation of my own that I always tell people, "I don't treat cancer, I treat cancer patients," and I think that's really important because as I mentioned, knowing the role of the pancreas in terms of digestion as well as in glucose control, these patients are challenging because they develop malabsorption and that is the reason palliative management or supportive management is a key element for these patients. Not only do we try to take the first step to help these patients, but these patient see me and the same day they see a26:43 into mp3 file http://www.yalecancercenter.org/podcast/feb1410-cancer-answers-saif.mp3 nutritionist, a social worker, and the same day I put them on certain medications that are important such as enzyme replacement. Sometimes we need to place someone on some other medication that makes this enzyme work better, but in addition to that, on the research side we are also studying these things. As I mentioned to you about the herbal medication we are studying, in that clinical trial we are trying to validate certain special criteria that could be very helpful in future science and research in pancreatic cancer to see how

we are improving the quality of life for these patients. And last but not least, I think family support is a key element because not only do you have to help the patient, but you also need to help the family that is going through this difficult time.Chu You just mentioned enzyme replacement, can you explain to us why enzyme replacement is a necessary part of the treatment approach for these patients?Saif It's important because when pancreatic cancer develops in the gland, either it's replacing the gland or it is causing what we call autocrine or paracrine effect on those surrounding cells. And what happens when the pancreas either is not producing enough enzymes or even if its producing those enzymes these enzymes could be of different chemical composition because of the effect of cancer, these patients have some obstruction of the bile duct, which is supposed to bring the bile from the gallbladder and the liver into the small intestine that helps the fat digestion. Keeping these three things in mind, it has been shown that placing them on a replacement such as pancreatic lipase, Pancrezyme, Creon, and many other such drugs, can prevent malabsorption and prevent weight loss in these patients. Interestingly, some small studies done at other centers have also shown that there is some survival benefit of adding these enzymes. We also learned that these enzymes don't work very well if you take them into the stomach, which has acidity. Therefore, giving a proton pump inhibitor such as Prilosec, Protonix, or those kinds of drugs, make these enzymes work better and prevent their destruction by the acid in the stomach.Chu Wasif, its amazing how quickly time has gone, I want to thank you for joining me this evening on Yale Cancer Center Answers. This really has been a terrific show reviewing for our listeners how to evaluate and treat patients with pancreatic cancer. We look forward to having you on a future show.Saif Thank you.Chu Until next week, this is Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week.If you have any questions or would like to share your comments, you can go to 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 for Connecticut Public Radio.