

Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week, doctor Foss is joined by Dr. Sajid Khan. Dr. Khan is Assistant Professor of Surgical Oncology at Yale School of Medicine and he joins us this evening for a conversation about surgical options for GI cancers. Here is Francine Foss.

Foss Let's start off by having you tell us a little bit about yourself. How long have you been at Yale and what was your training before you came here?

Khan I recently started working at Yale just this past summer and I am a surgical oncologist. I completed my general surgical residency at Oregon Health and Science University in Portland, Oregon and I completed my clinical and research fellowships at Memorial Sloan-Kettering Cancer Center and the University of Chicago. My clinical focus is primarily on gastrointestinal cancers. And my research focus looks at molecular and clinical features of patients with a low burden of metastasis or oligometastases, in order to identify patients who can truly benefit from a surgical resection. As a member of the Yale Department of Surgery, I was recruited by Dr. Robert Udelsman and Dr. Ronald Salem to extend the services of the Yale Section of Surgical Oncology to Bridgeport Hospital and the surrounding Fairfield County, and we hope that my presence there will allow individuals in the city of Bridgeport and Fairfield County in general more convenient access to Yale level surgery and to recapitulate the high quality of cancer care including the multidisciplinary care of our patients.

Foss That is a place where we can start off our discussion, can you integrate for us medical oncology, surgical oncology and the whole multidisciplinary approach at Yale Cancer Center, how does that all work?

Khan I am glad you mentioned that, one of the reasons I went into surgical oncology is because of the multidisciplinary care that is required to take care of each individual patient. Regularly patients that I see in clinic will be presented at a GI tumor board where experts in medical oncology, gastroenterology, pathology, radiology, genetics and social work, a whole team of people, collaborate together and discuss each patient and decide who will benefit from what kind of therapies, so it is not just the surgeon calling the shots or one

particular discipline calling the shots, it's all of us working as a team at provide care and I think that is a pretty valuable thing.

Foss As a medical oncologist, to me the surgical oncologist is oftentimes the first portal of entry, because a lot of patients with solid tumors present through a surgeon. Can you talk a little bit about that and how you first encounter a patient? What is that like and how do you make a referral from there to the other disciplines?

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Khan Many times the patient will have an incidental finding on a CAT scan for a trauma, or for a reason that is not cancer, and they did not even know it. If I see a patient in my clinic I present every one of my patients at our GI tumor board and we run GI tumor boards here at Yale-New Haven but we also run them at Bridgeport. I submit each patient and allow all the experts in the various disciplines of oncology to learn about the patient and then we decide as a team what the best thing to do for that individual is.

Foss Your major focus is GI cancers, can we backtrack and have you tell us a little bit about what those cancers are?

Khan The GI cancers that I treat are essentially all cancers of the gastrointestinal tract, and they include cancers of the esophagus, gastric cancers, gastrointestinal stromal tumors, which are cancers that we will talk more about later, which can occur in the stomach or the small intestine or other parts of the GI tract, pancreatic cancer and premalignant pancreatic tumors, colorectal cancer, liver metastases, hepatocellular carcinoma, cholangiole carcinoma, which is a cancer of the bile ducts, gallbladder cancer and colorectal cancer and thus far, if you were to ask me if there is a specific type of cancer I have seen more, there is actually a relatively even distribution of all of these cancers so far in my practice.

Foss Can you tell how common these cancers are? What is the most common of that group and what is the least common?

Khan I would say colon or rectal cancer are the most common within that group and one of the reasons for that is screening colonoscopies, and it has to do with cancers that are picked up on screening studies and colon cancer is

one of the GI cancers where we actually have a great screening modality which is a very good thing. Some of the cancers that are more rare are cancers of the bile duct, or what is called cholangiocarcinoma, and those are often picked up at a more advanced stage and the patient aren't often amenable to a surgical cure, which is unfortunate, so I think when we learn to have better screening modalities I think that will help pick some of these other cancers at an earlier time.

Foss Let's talk a little bit about screening since you brought it up, a colon cancer is one of the top cancers for both men and women in the United States, as you alluded to, and we actually do have screening tools that perhaps can prevent more advanced cases. Can you talk about that?

Khan As you mentioned, there are screening options available for some of the GI cancers but in my opinion there are not enough and I think we have to do better as a medical community in this arena because the earlier a cancer is detected, the better the chances are for cure. So a colonoscopy is an excellent example of a good screening modality for GI cancers. Unfortunately colon cancer is the only GI cancer where all individuals can undergo screening by a certain age and actually have

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some benefit. So all average risk patients should have their first screening colonoscopy beginning at the age of 50 and patients with an increased risk or high risk syndromes should be screened at an earlier age. Patients with Barrett's esophagus are recommended to undergo upper endoscopy screening for esophageal problems as well as esophageal tumors or malignancies and the recommendations vary based on the presence or absence of atypical findings, and the patients with risk factors of hepatocellular carcinoma are the third type of GI cancer that we have some sort of screening modality for. So hepatocellular carcinoma, or liver cancer, patients that are at risk of developing hepatocellular carcinoma, include patients with cirrhosis or from chronic inflammatory problems of the liver, which include hepatitis C and D, alcoholism, and non-alcoholic steatohepatitis just to name a few. I will quickly make a side comment, non-alcoholic steatohepatitis is a relatively newer entity that we are dealing with that is a type of hepatitis that patients can get from obesity and obesity is becoming a problem in this country, so I think it is something we should all be aware of. Going back to the screening, individuals with these kinds of risk factors should undergo screening liver ultrasound and alphafetoprotein levels, which is a tumor marker, every 6 months to 12 months.

Foss You just mentioned steatohepatitis in obesity, and with obesity as an epidemic in the United States, how should we be screening those patients? Should every patient when they go to their primary care physician after a certain age, who is obese, get these kinds of screening tests?

Khan I wish I had a great answer for you, but we have to find out what the appropriate way to screen for these individuals is. I think in the long run, for a lot of the screening studies, we are going to be able to identify certain risk factors and use in conjunction with the current modalities that we have such as ultrasound or some sort of GI study or an endoscopy to screen patients and find out who we can catch the liver cancer early enough, but I do not have a great answer for that Francine.

Foss Can we talk a little bit about colon cancer screening again? You mentioned that over age 50, people start getting colonoscopies unless they have risk factors. Can you talk about what those risk factors are that would indicate that people under age 50 should start getting screened?

Khan Some of the factors that increase an individual risks are individuals that have inflammatory bowel disease or Crohn's disease, or ulcerative colitis. So those individuals should talk to their physician or their gastroenterologist to ask about early screening. There are also patients, about 5% of patients with colon cancer, that actually have a known high risk syndrome and the two that we always think about are FAP or familial adenomatous polyposis, which is an individual that has thousands of polyps carpeting their colon, or HNPCC or what is called the Lynch syndrome. So those are high risk syndromes that also should be screened at an earlier age.

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Foss You mentioned Barrett's esophagus, and I wonder if you could clarify that for the audience, what does that disease do? Who does that occur in? And what is the screening that would be necessary if you have that?

Khan Barrett's esophagus is essentially a change in the histological features of an individual esophagus, and not to sound too technical, but the

esophagus generally is made of squamous epithelium and it looks different under a microscope and it actually looks different when a gastroenterologist is scoping a patient, and Barrett's esophagus is a risk factor for the development of esophageal cancer. The patients that have low-grade dysplasia have a higher risk of developing esophageal cancer, but not high enough where they need surgery. So the patients that have low grade dysplasia found in a background of Barrett's should undergo more frequent screening endoscopies. Those with high-grade dysplasia actually at that point, we are thinking, do they need an aggressive endoscopic intervention, or sometimes even surgery.

Foss It sounds like a lot of the cancers we are talking about could be picked up with appropriate screening, but can you tell us, in your practice, how often people come in with cancers that were not picked up with screening and just present with some manifestations of the cancer?

Khan I am a surgical oncologist and as a surgical oncologist a lot of times I do not see the patients that have very advanced disease. I am usually referred patients or meet patients that actually have a potential for cure, so I often see patients that are amenable to a surgical care, so I am probably not the best person to assess that question.

Foss If a patient does actually get to the point where they were picked up with screening and they actually have a cancer, can you talk about what the clinical presentation is for many of these patients? Do they have symptoms? What are those symptoms?

Khan This is a pretty broad question and there are different answers depending on the type of cancer that we talked about. Some are fortunate that they present with the screening modality and that is a good thing. Some are found incidentally on a CAT scan and that can be a good thing too, but unfortunately a lot of patients with gastric cancers present with disease that is too advanced to have a surgical cure and in the United States it is actually too often the case for patients with esophageal cancer, gastric cancer, pancreatic cancer, and cancer of the bile ducts. Some nonspecific symptoms of GI cancers, and I must stress that they can also be for non-cancer problems also, are weight loss, decreased appetite, or abdominal pain, but some specific symptoms in regards to particular cancers, are some patients with esophageal cancer will present with difficulty swallowing gradually, patients with gastric and esophageal cancer can present with upper abdominal discomfort or pain. The sensation of fullness or bloating after eating and they can also present at a primary care doctor with anemia, which is because of a chronic bleed from their tumor.

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Patient's with pancreatic cancer, cholangiocarcinoma, or cancer of the bile ducts, and liver cancer can present with jaundice, itching, yellowing of the eyes, or some upper abdominal pain or discomfort, and then we talked a little about colon cancer being picked up from screening, but it can also be picked up by patients that have bleeding from their rectum.

Foss How often can you actually make the diagnosis without surgery, or is the diagnosis made in many cases when you operate?

Khan That is a great question, a lot of times the diagnosis is made before surgery, or we have a pretty good idea, we do not know 100% of the time, I would say until the tumor or the structure that is of concern is out and the pathologist will look at that under a slide. However, that being said, CAT scans and MRIs are outstanding today and many times patients won't even need a biopsy. There are some specific findings that go along with particular GI cancers that the surgical oncologist or the radiologist will look at together and know that that is something to be worried about and sometimes we will take someone to the operating room without a tissue diagnosis and very suspicious, and they probably will have the problem that we were looking for in the beginning.

Foss Let's talk a little bit more after the break about some other specific surgical options and some of your research. We are going to take a brief break right now for a medical minute. Please stay tuned to learn more about surgical options for GI cancers with our guest Dr. Sajid Khan.

Medical

Minute There are over 12 million cancer survivors in the US right now and the numbers keeps growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and cancer survivors may face other long term side effects of cancer including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers like the one at Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute brought you as a public service by Yale Cancer Center, more information is

available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined today by my guest Dr. Khan and we are here discussing surgical options for GI cancers. We talked a little bit in detail about some of the specific kinds of GI cancer and your approach to those patients, but I wonder if you could step us through the whole process, so the patient comes in, they have a diagnosis of GI cancer, they see you, what happens next?

Khan That is a very important question Francine. I think the most important thing for a GI cancer

15:56 into mp3 file <http://medicine.yale.edu/cancer/podcasts/2013%201110%20YCC%20Answers%20-%20Dr%20Kahn.mp3>

patient, and I think this applies to a lot of other cancers too, is multidisciplinary care and that is actually one of the big reasons I chose to specialize in surgical oncology as opposed to other disciplines in surgery. In all solid tumors, specifically in relation to GI cancers, it cannot be emphasized enough that patients should all be assessed in a multidisciplinary approach and that is how myself and my partners at Yale Surgical Oncology treat all of our patients and this certainly holds true with all the patients I see at Bridgeport Hospital. Having the expert opinion of all disciplines of oncology provides patients with the best possible outcomes, and when I say multidisciplinary care, let me talk about what I mean a little bit more. I mean that experts from various disciplines of oncology regularly meet in a room and discuss each patient that we all see in our clinics with GI cancer, and all of us put our heads together and come up with the consensus opinion or consensus statement on what we think the best possible treatment for that patient would be. In some cases, that involves surgery first and then chemo and/or radiation therapy afterwards. Sometimes it involves starting with chemotherapy and/or radiation therapy first and then moving forward with a surgery later, and I think that is the trend for a lot of cancers these days, because it actually helps identify which patients will benefit from surgery and it also allows us to figure a little bit more out about the biology of the cancer we are dealing with.

Foss It is really important that you have all of these disciplines involved, particularly if it would benefit the patient to get one of these other modalities before you operate.

Khan Absolutely Francine.

Foss Let me ask a question about the evolution of surgery in the context of GI cancers. I know that there is a lot of laparoscopic surgery being done now for other conditions, and I am wondering, in the setting of cancer, are those kinds of relatively noninvasive approaches things that you are doing?

Khan They are things that I am doing, and my partners are doing as well. Many of the tumors can be dealt with minimally invasively, and laparoscopy is one aspect of minimally invasive surgery. Sometime if we see tumors of the pancreas, when they are at a particular location, they could be amenable to laparoscopic or minimally invasive resection, the same can be said of colon cancer. About 15 years ago every patient with colon cancer was treated with a laparotomy, or big abdominal incision, but now many patients with colon cancer can be treated with the laparoscopic or minimally invasive approach. So it is there but it does not mean we need to overstep our bounds with it either. Some patients, I think, are better off not having a minimally invasive approach a lot of times. There is a minimally invasive approach involved in a lot of our GI cancer operations, but sometimes it is involved in part of the operation where we will take a quick look with the laparoscope to make sure that the patient does not have any evidence of any distant metastases before forging ahead with a bigger abdominal operation so it is a balance and we should be aware of that.

19:09 into mp3 file <http://medicine.yale.edu/cancer/podcasts/2013%201110%20YCC%20Answers%20-%20Dr%20Kahn.mp3>

Foss Do you feel overall that GI surgery is tolerated better with the patients recovering quicker now-a-days due to some of the new techniques?

Khan I would say that and the big part of that is laparoscopy or minimally invasive surgery. In some operations that are well studied which include colon cancer and some operations to the pancreas with the laparoscopy, patients will end up leaving the hospital sooner, if they undergo a minimally invasive approach and patients will require less pain medication also if they undergo a minimally invasive approach.

Foss And also they will be able to start their other therapy, be it chemo or radiation or whatever else sooner I would presume?

Khan That is correct.

Foss You mentioned a tumor called a GIST tumor earlier and we have not talked about that one yet. I wonder if you could let us in on what that is?

Khan Sure Francine, GIST stands for gastrointestinal stromal tumors and it is a relatively uncommon cancer with about 5000 cases diagnosed each year in the United States. It is a soft tissue tumor as opposed to an epithelial tumor which is what we often see and it mostly occurs in the stomach, in 60% of cases, and 30% of the time it will occur in the small intestine and it can occur in other parts of the GI tract too. This is a good example of multi-modality treatment, so when the disease is not metastatic the treatment generally starts with a surgical resection that usually involves a wedge resection or a segmental resection of the organ that is involved and we just hope to take the tumor out with an intact capsule, pseudocapsule, without any lymph node dissection. So, it is not uncommon for GIST, we talked a little bit about minimally invasive or laparoscopic surgery before, it is not uncommon for GIST to be able to be amenable to laparoscopic resection because we are essentially just taking out a segment or a wedge of the tumor as opposed to an entire organ and that usually is a little bit easier to do laparoscopically, and myself and my partners at Yale actually try to do that when we can with GIST tumors when they are in a favorable anatomic location. So let's talk a little bit about multidisciplinary care here, so after the surgeon resects the tumor, the pathologist who is also critical in oncology care analyzes the tumor and what we care most about is the size of the tumor and what it looks like under the microscope. We look at those characteristics and decide if a patient will benefit from adjuvant therapy or a given therapy after surgery and what we think of here a lot of times is imatinib. It is worth pausing a minute to discuss imatinib for a bit. Imatinib is one of the most important cancer drugs available. It is a targeted drug and actually inhibits what is called a kit or tyrosine kinase receptor which is mutated in about 90% of cases of GIST. Imatinib was actually invented where I did my residency in Oregon and it is actually one of the first targeted drugs that was shown to specifically act

22:16 into mp3 file <http://medicine.yale.edu/cancer/podcasts/2013%201110%20YCC%20Answers%20-%20Dr%20Kahn.mp3>

in an identified mutation and that is what the signs showed initially, and within the last 10 years there have been trials to support that and it shows that patients that are treated with GIST with certain characteristics, will actually have a good clinical benefit and I guess the last way to manage GIST is that sometimes the tumor is too big and surgery is probably not the best thing to start with, it would involve a big operation that would resect organs

that if you can save it would be nice to do and sometimes patients were given the biologic therapy or the imatinib before surgery and the tumor will have a chance to shrink and then the surgeon can go ahead and do a less extensive operation, so that is a good example of multidisciplinary care and you can't have that unless all the experts in oncology are sitting in the room together discussing each patient and every individual.

Foss I think that the GIST story is particularly interesting because imatinib actually comes from my neck of the woods as a hematologist. It was originally developed for patients with CML that express the BCR-ABL and I am wondering, how did it get from hematology into GI tumors? How did that happen, did somebody identify the mutation and suggest that it might be useful in the GIST tumor?

Khan I would not be telling you the truth if I pretend I knew the entire story behind it, I do not.

Foss It seems interesting though that one can identify a pathway, this target is a specific pathway, molecular pathway, and it shows you that you can take these targeted agents from one tumor to another. Can you talk about other potential targeting therapies in GI cancer or are there other paradigms like this being developed?

Khan There are a couple of good ones and some of my research has been in colon cancer and a really good example is the use of cetuximab or panitumumab on patients with metastatic colon cancer. Essentially, the patients can have a mutation in what is called the KRAS gene which is a particular gene in colon cancer and individuals that do not have a mutation in that gene benefit from treatment with cetuximab because it actually targets this pathway. Another good example of this is patients with gastric cancer. The HER2 amplification is a big story in breast cancer but recently it has shown to be a big story in gastric cancer too. 24% of the patients with gastric cancer actually have HER2 amplification and they were given a drug that works in this HER2 pathway and they actually were found to have a good survival benefit. So this applies to different types of GI cancers and that is why Gleevec or imatinib, is such an important drug I think because it paved the way for the GI oncology community to try to recapitulate the use of it in other kinds of cancers.

Foss So you have actually done some work in your research looking at the molecular biology behind these tumors and metastases and how to deal

with that situation clinically? Can you tell us a little bit about what you have been doing?

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Khan I love talking about my research and so many times when patients have metastases they are actually not seen by a surgical oncologist and a lot of times the patients will need systemic chemotherapy and they are not surgical candidates, but there is a sub-group of patients with metastases that will benefit from a local therapy which can include a surgical resection or a stereotactic radiotherapy. And right now the way those patients are identified and selected for surgery is looking at clinical characteristics. But my research focus is looking at the molecular characteristics of the patients with this limited number of metastases, so called oligometastases. I was fortunate enough during my fellowship to be working for Ralph Weichselbaum and Sam Hellman in their lab and those are the two physicians that came up with the term oligometastases and we actually found that looking at certain molecular markers, if something called MicroRNAs, certain MicroRNAs were looked at and identified patients with a limited number of metastases and those are the patients that we hope to identify to treat them with surgical resection to try to use the combination, not just the clinical data, we would like to use molecular data in addition to clinical data to select patients for surgical resection.

Foss You are talking about these MicroRNAs. Can you just very briefly tell our audience what this is and the actual technique you use to detect these, do you do this in the tumor tissue and the metastatic tissue, how do you actually get that information?

Khan Technology is pretty advanced these days in molecular biology and some of the studies we've done involve actually taking the patient's tumor tissue, metastatic tumor tissue at times and sometimes we look at the primary tumor and actually examine each patient's tumor for these MicroRNAs and see what their expression of these MicroRNAs are and we compare the patients with good outcomes and the patients with bad outcomes, unfortunately and we try to look at MicroRNAs that are associated with a more favorable outcome. So it is true clinical translational research.

Foss Is this something that can be done in real time for the patients coming into your clinic now?

Khan Ultimately that is the goal, but right now I think it is still research, but ultimately that is the goal.

Foss You talked about patients who have only a few metastases and that one approach might be to surgically resect those. Can you talk a little bit about that? What is your strategy for those patients and how do you make that decision given that you do not have access to these MicroRNA data? What is your clinical decision making on that?

Khan A lot of it has to do with looking at clinical characteristics and a big part of that has to do with looking at the imaging. A good example for this is colon cancer that has metastasized to the liver. Patients that actually have colon cancer that has metastasized only to the liver and nowhere else should be seen by a surgical oncologist for consideration for surgical resection. We look at characteristics that will allow us to think if we can actually cure the patient because it is a big

29:06 into mp3 file <http://medicine.yale.edu/cancer/podcasts/2013%201110%20YCC%20Answers%20-%20Dr%20Kahn.mp3> surgery and you want to do the surgery if it is going to benefit the patient. So the patients with a low number of metastases, or metastases that are localized to one aspect of the liver, are people that are good candidates for this and lastly, I must mention, it is a long disease free interval.

Dr. Sajid Khan is Assistant Professor of Surgical Oncology at the Yale School of Medicine. If you have questions or comments we invite you to visit yalecancercenter.org where you can also get the podcast and find written transcripts of previously broadcast episodes. You are listening to the WNPR Connecticut public Media Source for News and Ideas.