00;00;00;02 - 00;00;30;14 WNPR (CT public radio voice) Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers. The director of the Yale Cancer Center, Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Dr. Winer.

Dr. Eric Winer Tonight, we are focusing on gastro esophageal cancers. These are really two separate cancers. 00;00;30;14 - 00;01;01;27 But as you'll hear, they're treated in very similar ways. And sometimes there's a bit of confusion between the two. They are relatively common cancers. Stomach cancer, for example, is the fifth most common cancer worldwide. And in the US, esophageal cancer is actually perhaps a bit more common. While not as common in the U.S. as around the rest of the world.

Dr. Winer 00;01;02;14 - 00;01;31;02 Gastric cancer is often diagnosed at an advanced age, making awareness, early detection and advancements in treatment ever so much more important. Our show tonight will focus on the progress being made in research and care. And we hope that this will be helpful to many of you. That being said, I'm well, I'm thrilled to welcome to the show our guest, Dr. Raghav Sundar.

Dr. Winer 00;01;31;24 - 00;02;01;11 Dr. Sundar joined the Yale faculty just under a year ago. He's a medical oncologist at Smile Cancer Center and an associate professor of medicine at Yale in the Cancer center. He has a relatively unusual path to us, and I'm going to let him describe that in just a minute. Rajiv, thank you so much for being here with us tonight on your cancer answers.

Dr. Sundar 00;02;02;03 - 00;02;33;20 Thanks for the introductions, Eric, and having me on. It's great to be here.

Dr. Winer So since I didn't get into it in my introduction, maybe you could tell us a little bit about how you got to Yale and where you're from.

Dr. Sundar Thanks, Eric. You're right. It is a little bit of an unusual story. So I was born in India and moved to Singapore to do high school, and I was in Singapore ever since I did my training in medical school and then specialization in oncology.

Dr. Sundar 00;02;34;05 - 00;03;05;26 I also did a special subspecialties training and experimental therapeutics and early phase clinical trials in the U.K., in the Royal Marsden, and then came back to Singapore to do a Ph.D. in gastric cancer. I was working as a translational physician scientist in this in Singapore, in the Singapore Gastric Cancer Consortium, which is a group of physicians, surgeons and scientists that were working together to answer the most difficult questions that were there in gastric cancer.

00;03;06;13 - 00;03;36;17 Dr. Sundar And a couple of years ago, my boss and mentee mentor, Dr. Pamela Kunz, approached me and we had a little bit of a chat and saw some opportunities at Yale. And one thing led to another. And

now I'm here. So I and I was going to say and you know, it's not terribly often that we have people recruited from around the world.

00;03;36;17 - 00;04;22;03 Dr. Winer And we heard about this from your boss, Pamela Kunz, who's been on this show before. And I will tell you that when we heard her talk about you, we were immediately enthusiastic.

Dr. Sundar Thanks. Yeah, it's been great. I spent a year here. A lot of the work that I'm doing is very similar to what I was doing back in Singapore, which is essentially seeing patients with gastroesophageal cancers, having opening clinical trials in this space for patients to have an opportunity to get new drugs and then translational work, discovering biomarkers and therapeutic targets that we try to develop new drugs for.

00;04;22;26 - 00;04;48;23 Dr. Winer And our audience may not be familiar with this, but the Singapore medical community and in particularly the medical oncology community is actually quite sophisticated. There are many extraordinarily well-trained physicians in Singapore. That said, I would bet that this feels like a very different kind of place to work and that there are probably more opportunities available to you here.

00;04;49;16 - 00;05;20;10 Dr. Sundar Absolutely. I think there are many similarities. And though the way things work, I think academic medical centers across the world often have more similarities and dissimilarities. But the opportunities that I've had at Yale have been fantastic. And it's been a really great experience so far.

Dr. Winer And just before we get into gastric cancer, the strategy of cancer, both in terms of epidemiology and in treatment and research, did you move here with a family?

00;05;20;23 - 00;05;45;09 Dr. Sundar I did. I moved with my wife and two children and they are having a great time settling down here as well. We have four seasons now, which we didn't have in Singapore.

Dr. Winer Yeah, that is true. Although I dare say that our orchids are not as beautiful as they are in Singapore, where they were really the flowering plants are just so lush.

00;05;46;24 - 00;06;22;07 Dr. Winer All right. So let's talk about gastric cancer and esophageal cancer. First. Maybe you could tell us why there's a both overlap and maybe a little confusion between the two.

Dr. Sundar Absolutely. So from for those who aren't very familiar with this area, the esophagus or the food pipe has two separate parts to it in terms of the way it looks under the microscope or the histology there is, the higher the upper part of it that looks very similar to the oral cavity or has a squamous lining.

00;06;22;20 - 00;06;53;07 Dr. Sundar And the second half of it that leads into the stomach has a lining that's more similar to the intestines or the column,

their lining. And that kind of determines the kind of cancers that develop in these other figures across the world and in the United States. The second half of the esophagus develops cancers called Adenocarcinomas and this type of cancer has a biology that's very similar to the rest of the stomach.

00;06;54;07 - 00;07;17;11 Dr. Sundar There is also some confusion because there's a separate entity called the gas through Sulfur Junction, which is right where the esophagus and the stomach join up. So this is right at the diaphragm, right between the chest and the abdomen. And that the cancer is there in the past used to have a different sort of belief on the way there manage.

00;07;17;11 - 00;07;47;05 Dr. Sundar But now we kind of think that all the adenocarcinomas that form from the esophagus all the way down to the stomach are treated in the same way. And so this has confused a lot of people in the space, but that's kind of what we're trying to align it globally to have some commonalities here.

Dr. Winer Yeah. And of all esophageal cancers, how many of them are squamous arising in the first two thirds of the esophagus and how many of them are adeno carcinomas?

00;07;47;15 - 00;08;23;15 Dr. Sundar Yeah, this actually varies globally. The squamous esophageal cancers are very much more smoking related cancers and they occur at a much higher incidence in Asia, particularly in China and Japan and Korea. The adenocarcinomas are much more common in the United States in the esophagus. These are more related to lifestyle changes and reflux. A higher body mass index or obesity leads to a higher rate of reflux, and that leads to functional cancers.

00;08;24;28 - 00;08;58;01 Dr. Winer And this audience has heard us talk about a high body mass index or obesity and its impact on cancer and is familiar with the fact that obesity is associated with an increased risk of actually 18 different kinds of cancers, of which esophageal cancer is one of those. So in the United States, we have relatively more lower esophageal cancer treated more like stomach cancer or gastric cancer.

00;08;58;29 - 00;09;26;11 Dr. Winer And if you combine all the lower esophageal cancers and the cancers that arise in the in the gastric lining in the stomach, I assume that that's a greater number than we see of the upper soft Jill cancers. Is that right?

Dr. Sundar Yeah, that's right. In fact, I mean, if you look at global numbers of stomach cancer, which is more common in Asia, is actually the fifth most common cause of cancer, as well as cancer related death globally.

00;09;27;07 - 00;09;49;16 Dr. Sundar And these are for cancers, actually, if you add them up to the stomach into the total number of deaths that are caused by this is actually very similar to the top few cancers like colorectal cancer or prostate cancer. So the numbers kind of add up. And this is us. This is a

problem. That's not just something, that's something that we do in the United States, but globally.

00;09;49;16 - 00;10;15;17 Dr. Sundar There's a very high burden of this disease that requires treatments. And we have new treatments that are coming up. That's pretty exciting.

Dr. Winer That's great. So just because we want to talk primarily about lower esophageal cancer and gastric cancer, maybe we can start by just talking very briefly about the upper esophageal cancers. And can you tell us a little bit about the treatment approaches for those cancers?

00;10;15;17 - 00;10;43;07 Dr. Winer And it's usually a multi modality approach that involves a number of different treatments and different types of doctors.

Dr. Sundar Right. So this part, because of the upper part of the esophagus, is right in the middle of the chest. It requires the best way to cure early stage esophageal cancer is to surgically removed these. But because it's right in the middle of the chest, these surgical approaches can be quite complicated.

00;10;43;17 - 00;11;07;28 Dr. Sundar And therefore we use treatments like chemotherapy and radiation to try and treat these patients pre-operative early to improve the surgical outcomes. And more recently and increasingly, we also talk about organ preservation, preserving approaches where we don't necessarily have to remove the upper part of the esophagus, but we can actually deal with it with just chemotherapy and radiation alone.

00;11;08;07 - 00;11;47;06 Dr. Sundar And that's typically how we treat the earlier stages of these cancers. In the advanced stages, then it's most likely treated with systemic therapies, with chemotherapy and immunotherapy being the most common backbones that we use to treat these cancers. And this is a cancer where immunotherapy has played a role. Absolutely. So this is interesting, the squamous cell cancers of the esophagus are quite sensitive to immunotherapy, and they've now been incorporated into frontline treatment, which means that anyone who is diagnosed with and an advanced esophageal squamous cell cancer would get both chemo and immunotherapy in the front line.

00;11;47;27 - 00;12;09;03 Dr. Winer And do those patients have the ability to go on and be cured?

Dr. Sundar We don't use the word cure so commonly in these sort of cancers because it's not something that we see very long many patients with long term survivals. But as with the immunotherapy in many other disease steps, we do have a small subgroup of patients who have long term survival.

00;12;09;03 - 00;12;36;11 Dr. Sundar Even at this in the stage four setting. So increasingly, I think we are a little bit more aggressive and a little bit more optimistic when these patients start treatment.

Dr. Winer But you're hesitancy about using the word cure is really for patients with advanced stage esophageal cancer and does not apply to patients who have early stage disease where you can use these treatments really with the hope that someone will go on and have a very long and healthy life.

00;12;36;22 - 00;12;58;20 Dr. Sundar Oh, yeah, absolutely. So I was definitely hesitant about using the word cure for advanced, but in the earlier stages we are talking about curative intent treatment and these species do have long term a good long term survival.

Dr. Winer And before we take a break, maybe you could talk a little bit about the symptoms that someone might have from esophageal cancer.

00;12;58;20 - 00;13;28;25 Dr. Winer And I think this probably applies equally well to upper and lower esophageal cancers.

Dr. Sundar Yeah. So the most common symptoms that we are taught about in textbooks is what we call as a difficulty in swallowing or dysphagia. This is very often the symptoms that patients with esophageal cancers have, but very often the ones that are diagnosed have very big symptoms of abdominal pain or low hemoglobin or bleeding in the gastrointestinal tract that's often picked up in blood tests.

00;13;29;05 - 00;13;52;24 Dr. Sundar And then they have endoscopies done and find these cancers, incidentally. So that's something that we'll probably talk about in the next part of the session is that identifying these cancers early are not very easy because the symptoms that patients present with with this sort of illness is not something that is very typical or specify for this cancer.

Dr. Winer Got it. 00;13;53;05 - 00;14;17;12 Well, we're going to need to take just have a very brief break. And when we come back, we will talk about the treatment of both lower esophageal cancers and gastric cancer, which is somewhat different from what we've heard about. We'll talk about some of the newest research in this area and we'll see where that goes. So we'll just be back in a minute.

00;14;18;01 - 00;14;46;29 WNPR (radio voice) Funding for Yale cancer answers comes from Smilow Cancer Hospital, where a Multispecialty team is dedicated to managing the diagnosis, evaluation and treatment of prostate cancer and other urology cancers. Learn more at Smilow Cancer Hospital dot org. The American Cancer Society estimates that over 200,000 cases of melanoma will be diagnosed in the United States this year, with over a thousand patients in Connecticut alone.

00;14;47;14 - 00;15;24;01 WNPR While melanoma accounts for only about 1% of skin cancer cases, it causes the most skin cancer deaths. But when detected early, it is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital to test innovative new treatments for melanoma. The goal of the specialized programs of research excellence in skin Cancer grant

is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improved diagnosis and treatment.

00;15;24;17 - 00;16;02;15 WNPR More information is available at Yale Cancer Center dot org. You're listening to Connecticut Public Radio.

Dr. Winer Welcome back to the second half of Yale cancer answers. I'm Eric Winer. And tonight I've been speaking with Dr. Raghav Sundar, a medical oncologist who treats gastrointestinal cancers at Smilow Cancer Hospital, focusing on esophageal cancer and gastric cancer or cancer of the stomach. Dr. Sundar, as he was telling us, did most of his training and spent his early career in Singapore.

00;16;02;27 - 00;16;32;24 Dr. Winer And much to our delight, he joined us here at Yale about a year ago. We talked in the first half about upper gastric and esophagael cancer, and now we're going to focus on lower esophageal and gastric cancers. These are adeno carcinomas, and we were talking earlier about the symptoms of esophageal cancer. I imagine that the symptoms of gastric cancers are a little different when people come to medical attention.

00;16;33;14 - 00;16;58;20 Dr. Sundar Absolutely. So the this the cancers in the stomach have a lot more of big sort of symptoms that they present with patients can have symptoms of abdominal pain or bloating. More commonly is these tumors tend to be easy to bleed. And so most of the time, the way we detect this is that folks would have a blood test to look at the hemoglobin and be found to have anemia.

00;16;58;26 - 00;17;30;15 Dr. Sundar And then they would get an endoscopy done which will detect the cancer. So it's quite important to consider that an iron deficiency anemia that's picked up that if there is a risk for stomach cancer, that they should get an endoscopy done to pick this up. There is no in the United States, there's no foremost screening that's done at the population level for some cancers in other parts of the world, like in Japan and Korea, where some cancers are a lot more frequent.

00;17;30;23 - 00;17;55;19 Dr. Sundar There are far more screening programs that are available, which is why here in the United States, most of the patients who get diagnosed with lower esophageal or gastric cancer are diagnosed at a later stage compared to those in other parts of the world.

Dr. Winer And can you comment on why gastric cancer is so much more common in Japan and in Korea?

00;17;57;13 - 00;18;38;28 Dr. Sundar We don't have a single answer for this, but there are multiple hypotheses around the kind of dietary intake that has been seen in Japan and Korea, especially to do with the high salt and fish salted fish diet. But these haven't had very cruise associations more commonly, and more importantly, probably the role of Helicobacter pylori, which is a bacteria that's present in the normal stomach in about a third to about half of folks all over

the world, but is known to be associated with the formation of gastric cancer in about 3 to 5% of people that have this.

00;18;39;08 - 00;19;08;18 Dr. Sundar And so there's a lot of focus now on trying to eradicate the Helicobacter pylori, which is often detected either using a breath test or an endoscopy, and this can be eradicated with a course of antibiotics.

Dr. Winer And isn't it also associated with an increased risk of ulcers in the stomach?

Dr. Sundar That's right. So though the way that Helicobacter pylori leads to stomach cancer is through an inflammatory process which can lead to ulcers as well.

00;19;09;24 - 00;19;39;09 Dr. Winer Got it. So how is it that we treat gastric cancer and lower esophageal cancer differently? What are the treatment approaches?

Dr. Sundar So I would broadly divide the treatment into the way we manage early stage cancers and then late stage cancers. The early stage cancers are very much similar in terms of a multimodal approach that we use in esophageal cancers, which surgery being the mainstay of treatment.

00;19;39;09 - 00;20;06;16 Dr. Sundar And the most important aspect of this is to use surgery to remove the tumor perceived slightly different from esophageal upper esophageal cancer is the role of radiation therapy, which is slightly less in gastric cancer. And we mostly use chemotherapy. Different chemotherapy drugs are what we call a combination chemotherapy use in a in a similar manner, both before and after surgery.

00;20;07;02 - 00;20;41;24 Dr. Sundar Very recently, there was a trial called the Matterhorn Trial that showed that the addition of immunotherapy to chemotherapy had its survival benefit. And so we have now started adding immunotherapy to chemotherapy even in the earliest stages of gastric cancer. Yet another cancer immunotherapy has led to an extension of life. And the list just keeps getting longer and longer, which is all the more reason why we need to figure out how to get around some of the side effects with immunotherapy, which many of many of our colleagues are working on very intently.

00;20;43;12 - 00;21;08;11 Dr. Winer And so a patient might receive chemo immunotherapy initially and then have surgery.

Dr. Sundar Absolutely. So the way we currently treat these patients is a combination of chemotherapy and immunotherapy, usually for about a couple of months, 2 to 3 months, after which they will go for surgery and after the surgery, then they'll finish up the rest of the chemotherapy and the immunotherapy as well.

00;21;08;20 - 00;21;44;11 Dr. Sundar And this has led to pretty high cure rates for earlier stages of gastric cancer.

Dr. Winer And why is it that radiation plays less of a role?

Dr. Sundar There are many theories around this, but I think mostly it has to do with the fact that the systemic therapy drugs have started to become a lot more effective in the past. A lot of the radiation was done to treat local disease, but the surgical techniques have improved as well, and therefore a mixture of just good chemotherapy with good surgery — does as well or are similar to with radiation therapy.

00;21;45;01 - 00;22;23;25 Dr. Winer I see. And are there genetic predispositions to gastric cancer?

Dr. Sundar Yes. So a majority of gastric cancers are sporadic, which means they're not hereditary nature. But there are a small percentage of folks who have a genetic hereditary mutation or a germline mutation that predisposes them to gastric cancer. The most common mutation is in the gene called CDK1, and patients that have a folks that have a mutation in Cdk1 have a higher risk of gastric cancer.

00;22;24;05 - 00;22;45;18 DR. Sundar I think more than the genetic predisposition is this concern about this rapid increase in the rates of gastric and esophageal cancers that we're seeing in younger patients below the age of 40. This is a phenomenon that we are seeing across multiple GI tumor types like colorectal cancer and pancreatic cancer as well. We're seeing the same phenomenon, gastroesophageal cancers.

00;22;45;18 - 00;23;26;19 Dr. Sundar I'm seeing a lot of younger folks getting diagnosed with this cancer and we don't really have a reason to explain this as of yet. A lot of us are doing a lot of research and trying to answer this question, but we don't really have a reason for this yet. And I think as you know, we're setting up a special clinical program very much connected to a research program to focus on young individuals with cancer, that is individuals under the age of 46, because both in the area of GI tumors and breast cancer and some other cancers, there does seem to be a striking rise in the risk of young people developing cancer.

00;23;27;06 - 00;23;54;10 Dr. Winer You know, earlier I think I asked you if there were genetic causes. I should have actually been clearer in the way I asked that question, because, of course, all cancer is genetic. It involves a change in the genome from a normal person's genome to the genome of the cancer, but not all cancers. And as you pointed out, most gastric cancers are not related to an inherited genetic problem.

00;23;55;18 - 00;24;20;12 Dr. Winer The interesting thing about this one, mutations, is they're also associated with an increased risk of a certain kind of breast cancer, lobular breast cancer. So many of these many of these genes changes that people inherited, people inherit can be associated with more than one type of cancer.

Dr. Sundar Yeah, absolutely. You're right about this. But as you said, most cancers are driven through genetic changes.

00;24;20;12 - 00;24;54;10 Dr. Sundar But one of the interesting things about gastric cancer is that a good proportion of them don't specifically have changes in the genome, but they have epigenetic changes or changes that are not specifically in the Danny, but in other aspects of the cell cycle itself that leads to the gastric cancer. In fact, one of the most exciting things that has risen from this whole concept is that we now have a targeted therapy against one of the proteins in gastric cancer called Claudin 18.2, which is not known to be an oncogene driver.

00;24;54;18 - 00;25;33;22 Dr. Sundar But we still have a drug that targets this protein and is now an effective additional treatment that we use for our patients with this cancer type.

Dr. Winer Wow. Interesting. You know, there's just so much that that we are we are learning when somebody has gone through treatment for gastric cancer. What kinds of problems do they have afterwards?

Dr. Sundar So patients that have gastric cancer treatment have to deal with not only the issues that they face with the cancer itself, which is very often abdominal pain, bloating in the abdomen and other sort of symptoms from a stomach cancer itself.

00;25;34;00 - 00;25;57;20 Dr. Sundar But they also have to deal with the side effects that they have from the chemotherapy and the other treatments that they are facing. The chemotherapy itself has symptoms of nausea and vomiting and specific to gastric cancer and other GI cancers is neuropathy. A lot of our drugs cause neuropathy and this is numbness or tingling sensation that you feel in the fingers and toes.

00;25;58;00 - 00;26;23;06 Dr. Sundar And this is very closely associated with a lot of the drugs that we use in gastric cancer.

Dr. Winer Yeah. Well, you know, we keep trying to develop drugs with fewer side effects that are more specific for the cancer in our last couple of minutes. Can you comment out on some of the most exciting research going on related to gastric cancer or for that matter, esophageal cancer?

00;26;23;15 - 00;26;48;22 Dr. Winer Where are we going and what can we be hopeful about in the not 30-year time horizon, but let's say in the next 5 to 7 years?

Dr. Sundar I think gastric cancer and esophageal cancer is one of the most exciting areas of development in identifying therapeutic targets and drug development. There are multiple new targets that have been developed in this space.

00;26;48;29 - 00;27;07;08 Dr. Sundar We just talked about it in point to where this is one of the first times we have a drug and a target that is first developed in

gastric cancer rather than most of the time. We have drugs that are developed for breast cancer or colon cancer and then are disallowed in gastric cancer. But we now have a drug that was first developed in gastric cancer.

00;27;08;00 - 00;27;36;08 Dr. Sundar We have other new therapeutic targets that have multiple drugs that are being tested. One of them is FGF ah to be, which we believe we're going to have a trial that's reading out in the next month that has another positive result. So we may have another therapeutic target. And this brings us to the idea of precision oncology in gastroesophageal cancers where we're identifying specific targets in the right patients to treat with the right drugs rather than blanket treating everyone with chemotherapy.

00;27;37;23 - 00;27;59;27 Dr. Sundar We also have more elegant ways in which we are using these targets. We don't necessarily treat them with just monoclonal antibodies. We have antibody drug conjugates. We have bispecific that are also being developed. And I think we have many of these clinical trials that are open for patients to consider enrolling in.

Dr. Winer Sure. And if I can just interpret for our audience for a second.

00;28;00;07 - 00;28;35;28 Dr. Winer Antibody drug conjugates are antibodies that are linked to a little dose of chemotherapy. So the antibody acts as the delivery truck and the chemotherapy comes in and ideal attacks the cancer itself and not as much as many of the surrounding tissues. And bispecific antibodies are antibodies that basically are two antibodies combined.

WNPR Dr. Raghav Sundar is an Associate Professor of Internal Medicine and Medical Oncology and Hematology at the Yale School of Medicine. 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. We hope you'll join us next time to learn more about the fight against cancer funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.