

Support comes from AstraZeneca, working side by side with leading scientists to better understand how complex data can be converted into innovative treatments. More information at astrazeneca-us.com Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about gastric cancers with Dr. Stacey Stein. Dr. Stein is an Assistant Professor of Medicine in Medical Oncology at Yale School of Medicine. Dr. Chagpar is an Associate Professor in the Department of Surgery and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center.

Chagpar Dr. Stein, maybe we can start off by talking about what exactly is gastric cancer?

Stein Great. So, it is a cancer of the stomach, and obviously, the stomach is attached to the esophagus, so some of the cancer start in the different parts of the stomach. Some of them start in the junction between the esophagus and stomach.

Chagpar And so, how common is this? I mean, most people have heard of breast cancer and colon cancer and prostate cancer, but not a lot of us know a lot of people who have stomach cancer.

Stein Right. So, stomach cancer worldwide is a big deal. About a million people are diagnosed worldwide every year. It is much less common in the United States than worldwide, but we still see - for stomach cancer alone - about 28,000 cases in the last year.

Chagpar And so, why is that? I mean, I recently got back from Bhutan and interestingly in Bhutan, stomach cancer and gastroesophageal cancer is one of their top cancers. Do we know what causes cancer, what might be leading to this worldwide variation in the incidence of this disease?

Stein So, there do seem to be some different effects and it is not all explained by the genetics of people from different background. It is much more prevalent in Asia. There probably is some link between potentially food or storage of food. In Japan, it is much higher. I do not think we completely understand that. There is also association with *H. pylori*, which is a bacterial infection that we have treatment for, but not everyone who has it knows that they have it, and even though *H. pylori* may be very prevalent, only about 1% of people with *H. pylori* infections wind up developing cancer from it.

Chagpar That is a good point because some people who have figured out that *H. pylori* is a causative kind of factor in gastroesophageal cancers have wondered about whether we should just randomly treat everybody, but if such a minority of *H. pylori* infection actually goes onto create cancer, that makes sense. How does gastroesophageal cancer present anyways?

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Stein So, it is interesting. The symptoms can be fairly nonspecific. So, sometimes people just feel uncomfortable after they eat, they may feel what we call early satiety, meaning they feel full when they have only eaten a small amount. Sometimes, they have some more bloating, they may have some heartburn symptoms. As the cancer gets more advanced, they may have weight loss and more fatigue.

Chagpar Does reflux symptoms, kind of gastroesophageal reflux, does that end up turning into cancer?

Stein So, most stomach cancers do not present with reflux, but some of the cancers at the very top of the stomach near where it meets the esophagus, the cardia or what we call the gastroesophageal junction, there is definitely a link between reflux so the acid splashing back up out of the stomach into the beginning of the esophagus that can lead to a lot of chronic inflammation, what we call Barrett's esophagus, and then it can eventually lead to cancer.

Chagpar So, I guess for people who may be getting reflux, because reflux is fairly common, especially when people are a little bit overweight or if they eat spicy foods or whatever, I mean there are a lot of people who get heartburn. When should they be concerned and what should doctors be doing to make sure that this is just heartburn versus this is heartburn that is leading on its way to Barrett's esophagus and cancer?

Stein Yeah, that is a good question. So, the gastroenterologist see these patients usually or the primary care physicians, and usually they will try a trial of medications that may decrease the acid production, and if the symptoms then go away or are well controlled, then the evaluation may stop there. But certainly, for patients who have persistent symptoms, usually they wound up having an endoscopy, which basically means that the gastroenterologist puts a probe down someone's mouth into the esophagus and gets to look around with a camera and see how the lining of the esophagus and stomach look.

Chagpar And so, if they see an abnormality, do they do a biopsy then, or?

Stein Yes, so they would do a biopsy and then our pathologist would let us know whether it looks just like a little bit of inflammation, whether an ulcer is forming, whether there are any cancer cells there.

Chagpar So, let us suppose there are no cancer cells, but it is starting to look like there is a little bit of inflammation, maybe this thing called Barrett's, at what interval should people be getting these endoscopies and biopsies, is that the recommendation, and how often should they continue on these anti-acid medications, I mean is that a lifelong thing to prevent cancer if you have reflux?

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Stein So, that is a good question. In general, you know, we do want people to be on medication to control the reflux, and we would repeat the endoscopy. Usually, depending on the findings, it could be as soon as 6 months or it might be at a year and not in every patient, but we often think of other lifestyle changes that patients could work on to maybe decrease the risk. So, it is not uncommon in the United States for gastroesophageal cancers that cancer right at the junction between esophagus and the stomach when there is reflux to sometimes be associated with abdominal obesity. So, we really then encourage people to try to exercise more frequently and have a weight loss plan.

Chagpar Is gastroesophageal cancer associated with smoking and alcohol?

Stein So, there are some associations with risk factors with lifestyle risk factors; when we think of, so the stomach and the lower part of the esophagus are similar types of cells lining it, but the top of the esophagus is a little bit different. So, when patients develop cancers in the stomach or the lower part of the esophagus, they are usually what we call an adenocarcinoma. The type of cancer that develops in the top part of the esophagus closer to the mouth are squamous carcinomas, which are more associated with alcohol and cigarette use, but certainly tobacco use does increase the risk of all types of cancer.

Chagpar Yeah. What about kind of smoked meats? I mean people have been talking about nitrosamines, does that increase your risk of stomach cancer?

Stein It does seem to increase the risk, and while not every study looking at lifestyle risks we have separated out by every disease, it certainly seems for cancers of the GI tract that having a healthier diet does decrease risk. We have certainly seen that from the colon cancer data in most detail, eating more fruits and vegetables, less smoked meats, processed meats, meat in general, more fiber in the diet seems to decrease the risk, also having a healthy weight.

Chagpar Alright. So, we understand that we can try to prevent cancer as much as we can by maintaining a healthy body weight, avoiding tobacco, avoiding kind of highly smoked, processed meats, but let us suppose you find yourself having abdominal pain, maybe you have some dark stool, and you start to get worried. Tell me about the workup of gastric cancer and how that all evolves.

Stein So, the symptoms for a lot of GI cancers are very similar to symptoms that could be non-cancer related, so often people present to their primary care physician, but if the pain is really acute, they may present to the emergency room. You know often the first part of the evaluation may include some modifications to see if the pain decreases, but then eventually people usually have an endoscopy like I described before with a camera to look, and then also other imaging like a CAT scan to get a sense of what is going in the belly.

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Chagpar Okay. So, let us suppose you do that and they look down and they see a lesion, an ulcer, whatever, and they biopsy it and lo and behold, it comes

back cancer. Is that how the diagnosis is made just on that biopsy?

Stein Right. So, there is two parts to the diagnosis – one is to have a biopsy so that we actually have pathology showing cancer cells and then the next important part is staging, meaning to figure out the extent of the cancer so then we can figure out what the best treatment option is.

Chagpar Now, I understand that staging is different for different cancers. So, some cancers like melanoma, it is really, you know, they look at not only the lymph nodes and the distant metastases, but they look at depth of invasion, whereas in breast cancer, we look at the size of the tumor. In gastric cancers, how is that done? What is a good prognostic factor, what is a bad prognostic factor? How exactly do we stage these people?

Stein Right. So, there are two parts to the staging. So, often when the biopsy is done, the patient may have had an endoscopy with a camera going down, but then we go back and we repeat the test again, but this time we also use an ultrasound probe, so that is called an endoscopic ultrasound or EUS, and that allows the gastroenterologist to actually look through the wall of the stomach or esophagus and determine how far through the wall the cancer spreads and that is important information to have. Then, they can also see the lymph nodes in the area and they could even potentially biopsy a lymph node through the wall using the ultrasound as guidance.

Chagpar So, right through the stomach they can biopsy a lymph node that might be hanging out near the stomach?

Stein Correct.

Chagpar And so, given all of that information, there must be kind of early stage gastric cancers and late stage gastric cancers. How are these managed differently?

Stein Right. So, we look how far through the wall it goes and then also we use the CAT scan to see if there is any spread of disease or metastases. So, the treatment is really different depending on the stage. If it is a very, very early stage, meaning that it is just at the most superficial part of the lining of the stomach or esophagus, sometimes the gastroenterologist can do the treatment themselves where they do a very local ablation or endomucosal resection, it is called EMR. And that is just for very superficial lesions. But for lesions that go thicker through the wall of the stomach or include lymph nodes, then we really have to think about surgery as a potential curative option, and sometimes that is with chemotherapy or chemotherapy and radiation. For patients who have more distant spread of disease, meaning that we cannot remove it all with a simple surgery to one area, then we really focus on chemotherapy.

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Chagpar And so, let us talk about the medium, the early stage, but it cannot

just be a mucosal resection. So, you know, we talk often in many cancers on this show about surgery and chemotherapy and radiation therapy and how these all work together and our perception is that sometimes, chemotherapy goes first and sometimes surgery goes first. How does it work in gastric cancer?

Stein Right. So, we do like to do some therapy for most cancers unless they are the very superficial kind. And there are some even that are a little bit more than just superficial that we do surgery and maybe not think about chemotherapy, but for the majority, we think about doing another treatment, and the reason for that is that we know that if we do surgery alone, the recurrence risk is high, so the assumption is that there must be some cells that were left behind and we really want to eradicate those cells around the time surgery to give patients the best chance at a cure. So, the treatment is a little bit different for esophageal cancer versus gastric, but the treatment for gastric cancer is usually chemotherapy before and after surgery, and then with esophageal cancer, we are usually also including radiation before the surgery.

Chagpar Great. Well, we are going to learn a lot more about all of these treatment options and how really the field is moving forward as we hope it is right after we take a short break for a Medical Minute. Please stay tuned to learn more information about gastric cancers with my guest, Dr. Stacey Stein.

Medical Minute Support comes from AstraZeneca, dedicated to advancing options and providing hope for people living with cancer. More information at astrazeneca-us.com. This is a Medical Minute about head and neck cancers. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment. Clinical trials are currently under way to test innovative new treatments for head and neck cancers and in many cases less radical surgeries are able to preserve nerves, arteries and muscles in the neck, enabling patients to move, speak, breathe and eat normally after surgery. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

Chagpar We are here talking about treatment advances for gastric cancer. So, right before the break, Stacey, we were talking about gastric cancers. These are the ones that are primarily in the stomach, and we talked about the fact that the majority of these gastric cancers are the ones that are not super superficial. So, they are not the ones that can be locally ablated by a gastroenterologist, but really require multimodality therapy – surgery plus chemotherapy often, and you mentioned that in the case of gastric cancer, chemotherapy is often sandwiched, you will start with chemotherapy, you will then do surgery and then you will finish with more chemotherapy. Why is that? In many other cancers, like breast cancer for example, we try to put all the chemotherapy upfront or all the chemotherapy out back, is there an advantage for the sandwich technique in gastric cancers?

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Stein You know, that is a good question. I think some of it is historical on how the first clinical trials were evolved and then it showed a benefit and that has become the paradigm for this type of cancer, but you are right, in many cancers, we are moving a lot of therapy to the front and for esophageal cancer, we give all the chemotherapy and radiation upfront. There really has not been a recent trial that looked at doing all of the therapy upfront versus sandwiching it this way, but this is the way we do it. Historically, then kind of the paradigm for this type of treatment.

Chagpar Okay, I was just curious. What about radiation, you mentioned in esophageal cancer, there is chemotherapy and radiation given upfront before surgery - how does radiation fit in to gastric cancers?

Stein Right. So, there have been studies looking at the role of radiation in gastric cancer also, where all the treatment is given upfront, and then there has also been this perioperative approach where the chemotherapy is before and after the surgery, and you can give either treatment. Usually, we focus more on radiation for cancers that are close to the junction between the stomach and the esophagus.

Chagpar Is that just because it moves less so that there is less toxicity because the stomach is more floppy than the GE junction, or is it because just radiation is not as effective in gastric cancer as it is in esophageal cancer?

Stein It seems to be more effective in the esophageal part.

Chagpar So, in terms of surgery for gastric cancer, does that mean the people's whole stomach needs to be removed?

Stein Not necessarily. It really depends on the location of the tumor and extent and the lymph node involvement. So, often patients can have what is called a partial gastrectomy where only some of the stomach is removed as opposed to the whole stomach removed, and as much as possible, we try to limit the amount of resection because we want patients to be able to recuperate well and be able to eat after the surgery.

Chagpar I would imagine that a lot of patients lose a lot of weight with that surgery. It sounds almost like of the surgeries that we hear about for weight loss surgery, is that true?

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Stein So, it is hard to maintain weight after a surgery like this. Patients often have to adjust to what I call a new normal. So, after big surgeries to the GI tract, often patients have to eat smaller meals more frequently, sometimes they need a lot of nutritional support right after surgery. Sometimes, at the time of surgery a feeding tube gets placed below the level of the surgery so that they can have nutrition supplements as they are kind of learning to re-eat. It is very

important to have a good kind of muscle store and protein store before going into a surgery and sometimes because of the tumor and location, people are having a hard time eating. So, we always include a nutritionist in our planning and we really try to educate the patient about how many calories they should be eating and really maintaining their nutrition.

Chagpar Yeah. Because I would think that, you know, the stomach is involved in absorption and vitamins and all kinds of other things that you need to think about, too.

Stein Right. So, we do have to think about the absorption certainly – one vitamin in particular is vitamin B12 that gets absorbed there and not in other parts of the GI tracts, so it is not uncommon for patients to need a supplement often in a shot form for some time after their surgery.

Chagpar Cool. So, let us talk more about chemotherapy, which I know is your expertise. Tell me more about chemotherapy. I mean, I think in so many cancers, the way I think of it is that there are some chemotherapies that are just kind of like the machine gun, and it goes and it kills all the rapidly dividing cells, but more and more, now we are beginning to find the shotgun, who can kind of target exactly where the cancer cells are and kill off those really trying to spare other tissues and other cells damaged. How are things going in gastric cancer?

Stein So, it has been exciting. We have had a couple of advances that are very encouraging. So, traditionally, we have used the standard chemotherapy drugs as you would say the big guns and while they have had some benefit, they have not been very effective, right – we are not curing every one that we treat with early cancer and even patients, especially the patient with metastatic disease, we know those treatments only last for a certain amount of time and then the cancer starts to grow in spite of those medications. There have been a few important drug targets that we found in gastric cancer. So, one is we found that about 20% of our patients with gastroesophageal cancer have what is called a HER-2 amplification. So, we already knew about this from breast cancer years before, and then it was found that this is actually relevant to this disease also, so we basically recopied some of the breast cancer studies and we were able to show that there was a benefit of giving the antibody trastuzumab to patients with metastatic disease. We also did a study where patients got chemotherapy and radiation before their surgery and half the patients got trastuzumab and half did not, and that study finished a while ago. We participated in that study and I think this year we are going to finally see the results of that study.

Chagpar Yeah, fingers crossed. It is always so exciting when patients and clinicians participate in clinical trials that potentially can move the field forward and it always the hardest part I find to wait for results to come out.

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Stein Yeah. Well, the study took a while to wait because the patients went through surgery and then they have been followed for a while, so I am eager to get the results.

Chagpar What else is on the horizon in gastric cancer?

Stein Right. So, very exciting, we finally have immunotherapy options available for our patients. So, this past year the results of the study with pembrolizumab, one of the PDL1 drugs so this is an antibody that targets a receptor on cells, it helps stimulate our white blood cells, so our own immune cells to attack the cancer and recognize it as foreign. Actually, this was presented by our cancer center director, Dr. Fuchs, at our big national meeting, and basically we saw that this study looked at patients who had metastatic disease, they had gotten at least a few different types of chemotherapy and then went on this study to see the benefit of the drug. And it seems that the responses were higher in people whose tumor tested positive for PDL1 and there was close to about a 16-18% response rate in those patients, and then the FDA in September approved the drug, pembrolizumab, for these patients who had already gotten some chemotherapy and tested positive for PDL1.

Chagpar So, that is really exciting. And I think as in so many clinical trials, things kind of start in the metastatic setting where so now you that trastuzumab might be really effective for HER2 positive gastric cancer, and pembrolizumab might be really effective for people who have been pretreated, who have a PDL1 receptor. But what about, are any of those therapies being considered kind of upfront before the disease has spread all over your body?

Stein Right. So, the trials are moving up looking at patients who are getting diagnosed at first. Also, we are looking at every patient to test them for what is called microsatellite instability, so we know that those patients have a lot more mutations in their tumors and seem to respond much better to immune therapy, so we are always looking for those patients, and most excitingly we are really trying to figure out why do only some of our patients respond to immune therapy and how do we get the other patients to respond to immune therapy. So, there is a next wave of trials that are what we call platform studies. So, they are able to move in different combinations of treatment as they kind of come through drug development. So, we are looking at combinations of immune therapy plus other drugs that may modulate the immune system to try to see can we get more responses from patients who may not have responded to just the pembrolizumab alone.

Chagpar So, is this just for the PDL1 patients or is it for other patients who might have also responded to immunotherapy if they had pick whatever, if they are MSI or if they have some other drug on board or whatever?

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Stein Right. So, we do not know. For the pembrolizumab study, actually 6%

of the PDL1 negative patients still had a response. So, I think there is hope right that we will be able to find alternative treatments that we can get more patients to respond including the PDL1 negative patients.

Chagpar Cool. So, what is the overall prognosis of these patients with gastric cancer? I mean, is this is a really bad disease, do people die?

Stein So, unfortunately, we cannot cure everyone with this disease and as the stage increases of the tumor, then the survival decreases. So, one of the numbers we often think about in cancer is what we call 5-year survival, meaning from the time of someone's diagnosis, how are patients doing 5 years forward, and we know for the patients with much more local disease, about two-thirds of patients are alive at 5 years.

Chagpar That's not bad.

Stein Right. They may or may not still be getting treatment. When the disease becomes more regional with lymph nodes that are involved, that number decreases to more like a third of patients are still alive at 5 years. Unfortunately, when patients have metastatic disease, even though we are trying to expand the number of treatments, unfortunately that number becomes all the way down to about 5%. So, there is a lot of room improvement and everyone in this field is really excited about getting more clinical trials, more good treatment options into the clinic so that we could really improve those numbers.

Chagpar So, one of the things that you mentioned was especially with regards to pembrolizumab was it was approved for people in that study who had been treated with multiple lines of therapy. So, one of the questions that I always have is, you get a treatment, maybe it works and maybe it does not work so well, how many of these lines of treatment do you go through? I mean, when do you decide that you are going to try something different and how do you decide what the different thing is?

Stein Right. So, that is why once we see some benefit in a trial, we really try to move those treatment options earlier into the treatment algorithm so that patients can get a benefit upfront. I think the question will be for patients who are newly diagnosed with metastatic disease, do we want to give them immune therapy alone upfront, or do we want to give a combination of chemotherapy and immune therapy. Right now, we do have more than one line of treatment available to patients -- we have different chemotherapy drugs, we also have a drug called ramucirumab, which is an antibody that targets blood vessel formation in tumors, and that has been shown to be somewhat effective by itself or in combination with chemotherapy. So, while we do have different lines of therapy, it is not an exhaustive list and certainly if there is something that is showing potential good effect with less side effects, we really want to try to move that up towards the initial therapy.

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Chagpar So, how do you decide, I mean, if you are sitting there and you have got metastatic gastric cancer and you have just told us that 5-year survival rate is single digits, you want to hit that with everything you can to try to improve that survival rate number. You want to be in that 5%. So, is it better to kind of take everything upfront or is it better to go one by one?

Stein So, most of the chemotherapy regimens are 2-drug regimens. Sometimes, before surgery we use 3-drug regimens, but they are more difficult to tolerate. So, usually, we would start with a 2-drug regimen, we get scans frequently so we can keep reassessing how someone is doing and then as we get results, we try to go to next best option.

Dr. Stacey Stein is an Assistant Professor of Medicine in Medical Oncology at 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. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer right here on WNPR.