

Dr. Jill Lacy, Understanding Stomach Cancers July 25, 2010 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. 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 and the phone number is 1888-234-4YCC. This evening Francine is joined by Dr. Jill Lacy. Dr. Lacy is an Associate Professor of Medical Oncology at Yale School of Medicine and she is an expert in the diagnosis and treatment of gastric cancers. Here is Francine Foss. Foss Let us start off by having you define what gastric cancer is? Lacy Gastric cancer is a malignancy that grows in the stomach, and actually there are a few different types of stomach cancers. There are some rare types, including gastric lymphomas, and these are tumors of lymph tissue often caused by bacteria and interestingly, can often be treated with an antibiotic. There are endocrine tumors, called carcinoids, and they are often very slow growing, almost benign tumors, that we often can ignore, but when we talk about gastric cancer or stomach cancer we are most often referring to the most common type of stomach cancer called adenocarcinoma of the stomach. These are very common cancers worldwide. They grow in the inner most superficial lining of the stomach wall. Worldwide, their incidence is about a million and gastric cancer is actually the number two cause of cancer related deaths after lung cancer. I would mention that there are some interesting epidemiologic features in the United States, the incidence of gastric cancer, adenocarcinoma, has been steadily declining since about the 1930s, so we are now down to about 22,000 cases a year with about 12,000 deaths per year. But what's of some concern is that in the past two decades or so there has been a spike in stomach cancers that are located close to the esophagus. We call these proximal gastric cancers or cardia cancers and unfortunately these tend to be a little bit more aggressive and have a worse prognosis than the gastric cancers that are further down in the stomach. We do not know why we are seeing this mini epidemic in these proximal gastric cancers, but we know that the risk factors appear to be similar to those for esophagus cancer; obesity, high BMI (body mass index), acid reflux disease, and preponderance in males over females, and again tobacco is a risk factor. Foss Jill, we hear a lot about antacid and there are a lot of advertisements in commercials on TV and in magazines about acid reflux disease and the use of antacids. I am wondering, is that really happening because of this increased risk in reflux and gastric cancer and does that actually help to prevent gastric cancer? Lacy I think it's very unclear as to whether acid reducing therapy influences the incidence of these proximal gastric cancers I think that's an area of active investigation. 3:33 into mp3 file <http://yalecancercenter.org/podcast/july2510-cancer-answers-lacy.mp3> Foss Can you talk a little bit about differences in terms of age and race, are there certain predispositions for gastric cancer other than the ones you mentioned? Lacy As I mentioned, in the United States there is preponderance in males, it is a disease of the older, middle aged and elderly. The median age is around 65 to 70 for gastric cancer, a little bit younger for the proximal gastric cancers. There is

tremendous geographic variability in the incidence of gastric cancer worldwide, so for example, there are very high incidence areas in East Asia, in particular Japan, in areas of South America in the region of the Andes Mountains and in Eastern Europe, so some of this may be ethnic, some may be environmental, we do not fully understand those marked geographic differences in incidence. Foss You mentioned alcohol and tobacco as being risk factors. Are there other dietary risk factors? Lacy There have been a large number of epidemiologic studies looking at the relationship between diet and gastric cancer and so the weight of evidence supports an increased risk of gastric cancer in areas of the world where the diets are high in salted foods, cured and smoked foods, and pickled foods. Conversely, diets high in fresh fruits and vegetables appear to be associated with a decreased risk of gastric cancer; that data is pretty solid in terms of those relationships. What is probably much more important than diet in terms of risk factors for gastric cancer is infection with the bacteria called *Helicobacter pylori* or *H. pylori*. *H. pylori* is a bacteria that's very common in our environment and it tends to infect the lining of the stomach and it can cause a number of stomach diseases including peptic ulcer disease, gastric ulcers, inflammation of the lining of the stomach or gastritis. We mentioned lymphoma before, it is a causative agent of stomach lymphomas and importantly, it is a major cause worldwide of gastric adenocarcinoma. Probably 40 to 50% of gastric cancers worldwide are related to *H. pylori* infection. Foss How does one actually know if they have *H. pylori*? Lacy Most people who have *H. pylori* have no symptoms. They do not know they have it and it will cause no problems, so that is the good news. There is really a very low incidence of gastric cancer in individuals who harbor *H. pylori*, but some of the symptoms that can be associated with *H. pylori* are stomach symptoms of indigestion, dyspepsia, high acid feeling, abdominal pain and obviously if one is experiencing symptoms like that, that should be discussed with one's primary care provider or one should see a gastroenterologist. Foss I know that in the case of gastric lymphoma just treating the *H. pylori* is often enough to eradicate the lymphoma, is that true for the other kinds of gastric cancer if you treat the *H. pylori*? Lacy For adenocarcinoma, caused by *H. pylori*, once you have carcinoma treating the *H. pylori* will not7:27 into mp3 file <http://yalecancercenter.org/podcast/july2510-cancer-answers-lacy.mp3> reverse that process. It is not an effective treatment for adenocarcinoma as it is in lymphoma, so that is a major difference. Foss Can we talk a little bit now about the diagnosis of gastric cancer? Lacy Patients are generally going to be diagnosed by a procedure called endoscopy and a directed biopsy of an area of abnormality on the inside in the stomach. Endoscopy is done by a gastroenterologist and it involves putting a flexible tube down the esophagus into the stomach. There is a bright light and a little camera on the end of the tube and the gastroenterologist is able to visualize the inside of the stomach with pictures that are projected on a TV monitor, and then if there is an abnormality that is visualized, the gastroenterologist can easily take a directed biopsy through the endoscope of that area and in general that's how we get the diagnosis of stomach cancers. Foss Is there any specific blood test that can be used? Lacy Not really. There is nothing specific that gives us a defini-

tive diagnosis of gastric cancer. You need to get a biopsy and that is generally done via endoscopy. Foss And once you have a diagnosis through endoscopy and biopsy, what are the next steps? Lacy In terms of the treatment of gastric cancer, treatment is going to be dictated by the extent of disease, whether it's localized to the stomach and surrounding structures, or whether it has spread to distant sites such as liver, the lung, or other areas in the abdomen, and so the initial evaluation involves determining the extent of disease and we in oncology call that staging the patient. Staging always involves a CAT scan, which gives pictures of the entire body and allows us to see whether there is distant spread. What is also very important in staging gastric cancer is a procedure called endoscopic ultrasound, or EUS, and again this is a procedure that involves putting an endoscope down into the stomach and in this case there is an ultrasound transducer around the end and one can generate very, very detailed pictures from ultrasound of the layers of the stomach and it allows one to see how deeply into the wall of the stomach the cancer has penetrated. That gives us some information about stage. Endoscopic ultrasound also allows us to look at the lymph nodes around the stomach and to see whether those lymph nodes or lymph glands may be involved with cancer as well. Foss Just to reassure our audience, when a patient undergoes this kind of endoscopy or ultrasound procedure, are they awake or are they sedated? 10:24 into mp3 file <http://yalecancercenter.org/podcast/july2510-cancer-answers-lacy.mp3> Lacy They are minimally sedated, this is a minimally invasive procedure, so there is some mild sedation and patients are likely sleeping through this procedure. Foss After getting the scans and determining how extensive the disease is, how do you make the next decision about how to treat a patient? Lacy Again, treatment of gastric cancer, like many cancers, is driven and dictated by the stage, so the extent of disease and how far it has spread, and that is determined by those staging procedures that we just went through, a CAT scan and an endoscopic ultrasound. Staging goes from 1 to 4, so for patients who have stage four disease, that would be disease that has spread to distant sites, for example, to the liver or lung, and those patients we generally would treat with palliative chemotherapy. They would not be a candidate for a curative surgical procedure; however, patients with lower stage disease, stages 1, 2, and 3, in general those patients will be going on to some kind of surgical procedure, which hopefully will be definitive and curative. Foss Given that more patients are having endoscopies now for various reasons, are we picking up more cases of gastric cancer earlier? Lacy Certainly in Japan, where they have a national screening program that involves actually looking at the lining of the stomach with Barium and X-rays, 40% of patients are diagnosed with what we call early stage gastric cancer. In the United States, we don't recommend any kind of routine screening as we do for colon cancer, for example, with colonoscopy, so most endoscopies are done in the setting of someone having some type of symptom. Therefore, we are not picking up gastric cancer as early stages as much as we would like. Most patients present with stage 2, stage 3 and stage 4 disease as opposed to stage 1 disease. Foss We have talked in the context of colon cancer about the virtual colonoscopy. Is there a virtual endoscopy yet? Lacy Not yet, not for gastric cancer. Now one has to go through that procedure. Foss

In patients say who are smokers and drinkers are those the kinds of patients who perhaps should think about getting screening procedures done? Lacy Again, there is no recommended mass screening for gastric cancer. Screening, however, can be individualized so if you have a patient that is at particularly high risk, and risk factors would be someone who has had documented H. pylori infection and abnormalities on endoscopy, someone who has a strong family history of gastric cancer, someone who has previously had gastric polyps removed that are premalignant, or someone who has known long standing inflammation of the lining of the stomach, gastritis, that's a risk factor. Those patients perhaps should be regularly screened with endoscopy. Foss I am glad you brought that issue up about family history. Are there genetic syndromes that are associated with gastric cancer? Lacy Most cases of gastric cancer are not genetic, but there are a few genetic syndromes that are associated with a marked increase of gastric cancer. There is a familial gastric cancer syndrome where generations after generations of patients are afflicted with gastric cancer. We actually think that Napoleon was part of a gastric cancer family. He died of gastric cancer as did one of his parents and grandparents. So those patients obviously are very high risk and not only should they be screened, but if the diagnosis is made and it's made through genetic testing, consideration of a prophylactic total gastrectomy should be made. A familial cancer syndrome that is associated with colon cancer is called the Lynch syndrome and in those families, there is also an increased risk of gastric cancer. Those family members probably should be screened not only with colonoscopy for colon cancer, but also upper endoscopy for gastric cancer. Foss This has been very informative. We are going to take a short break now for a medical minute. Stay tuned to learn more about therapies for gastric cancer with Dr. Jill Lacy. Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am here today with my guest with Dr. Jill Lacy who joins us to talk about gastrointestinal cancer. Jill, we talked a lot about the epidemiology and the diagnosis of gastric cancer. Can you tell us, once a patient is diagnosed and comes into the system, say into Yale Cancer Center, is there a multimodality approach for this disease? Lacy Yes, that's really been one of the major advances in the field. Up until about 10 years ago gastric cancer that was non metastatic and localized to the stomach and surrounding structures was treated with removal of the stomach, or part of the stomach, and in many cases that was definitive and curative therapy, but unfortunately even with the most optimum surgery in the United States more than 50% of patients who had undergone surgery for gastric cancer would have a recurrence, and when gastric cancer does recur, in most cases, it is fatal. What has changed has been the appreciation that the use of so called adjuvant therapies in addition to surgical resection can markedly improve the prognosis and cure rate for patients with gastric cancer. There have been several studies conducted here and in Europe and Asia that have shown that the administration of chemotherapy either before or after, or simply after surgical resection, or the use of radiation with chemotherapy after surgical resection, or

in some cases prior to surgery, can increase the overall cure rate by about 10% to 20%. The management of gastric cancer that is localized has really evolved from being exclusively a surgical disease to being a disease where multimodality therapy is critically important in maximizing the chances for cure. When we are faced with the patient who does not appear to have metastatic disease and is going to be a candidate for surgical resection, it's critically important that all the physicians that are going to be involved meet together and discuss the optimum management for the patient. That would be the gastroenterologist who has done the staging with endoscopy, the surgeon obviously, the medical oncologist, and radiation oncologist. At Yale we have a tumor board that meets once a week and we discuss all new cases of gastric cancer and come up with a treatment strategy that will involve multiple treatment modalities and there is often a lot of discussion about the most appropriate sequencing of surgery, chemotherapy, and radiation.

Foss Can you just let us know, on a national level, the NCCN guidelines for the treatment of gastric cancer in the resectable setting? What are the recommendations?

Lacy There actually is more than one recommendation. For patients with what we call resectable disease, a disease that has not spread to distant sites, one option is for patients to receive chemotherapy before surgery then go on to resection and receive additional chemotherapy after surgery. Second option is for patients who underwent an initial resection of their tumor upfront, gastrectomy, those patients should receive post operative adjuvant therapy and generally that's going to be radiation with chemotherapy, and then in patients who have gastric tumors that are very close to the esophagus or growing into the esophagus, those patients can be managed with one of the prior two approaches, or alternatively with radiation and chemotherapy prior to surgery, so it is a little bit complicated. There are a couple of different options and sequences and that's why a discussion in a tumor board format can be very helpful in optimizing management for patients.

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Foss Would you ever do surgery on a patient who has metastatic gastric cancer?

Lacy Generally when we are dealing with metastatic gastric cancer and we know that upfront from the staging evaluation, from the CAT scan or the endoscopic ultrasound, we would not do a gastrectomy, it's a big operation and it would potentially delay the time to starting chemotherapy; however, there are some settings where we do need to do surgery and that would be someone who presents with sort of catastrophic pictures such as perforation of the stomach or massive bleeding, those patients would go to surgery for palliative gastrectomy even in the metastatic setting.

Foss Can you tell us a little bit about the standard chemotherapy for gastric cancer?

Lacy This is a work in progress, I would say. There are a number of multi-drug regimens usually at least two drugs, in some cases three drugs, that appear to have approximately equivalent efficacy in controlling the disease and so one chooses the regimen based on the side effects and whether or not we think a patient would tolerate one drug over another.

Foss How long does the adjuvant chemotherapy go on for, how many months?

Lacy When we are using adjuvant chemotherapy in patients who are candidates for surgery, the protocol is 9 weeks of chemotherapy with a three

drug regimen prior to surgery, then surgery, then recovery from surgery and then an additional nine weeks, so it's 18 weeks of chemotherapy.Foss At the end of that is a patient essentially disease free for a long period of time?Lacy In the United States the overall cure rate with that kind of approach, taking everyone into account, is about 40%, so we certainly still have room for improvement.Foss It sounds like we have room to develop additional therapies in gastric cancer as well and I know Jill that you have been on the forefront in your research in looking at novel approaches for gastric cancer, can you tell us what's happening?Lacy There have been some very exciting developments in recent years in gastric cancer, and this is coming from lots of science that is now defining what the mutations and the molecular lesions or molecular abnormalities are that are causing gastric cancer, and so the hope is that by identifying these mutations and these molecular lesions that we will be able to use so called targeted therapies, therapies that specifically target these molecular abnormalities. We will be able to incorporate these targeted therapies into the treatment of gastric cancer. We are already doing this in some other cancers, in colon cancer, lung cancer, and breast cancer, and now I think we are beginning to see that we are going to be able to apply this type of approach to gastric cancer.24:21 into mp3 file <http://yalecancercenter.org/podcast/july2510-cancer-answers-lacy.mp3>Foss One of the drugs that you are using for gastric cancer is a drug that we use in breast cancer, Herceptin?Lacy This is very recent, and very exciting data. In gastric cancer about 25% of tumors will express or over express a large amount of a protein on the surface of the tumor cell called HER2 or HER2/neu and this protein has been a target in breast cancer for an antibody called Herceptin and Herceptin has been widely used in a subset of breast cancer patients for many, many years with great efficacy. And what we learned within the last year is patients with gastric cancers, again it is about 25% who express this protein HER2/neu, if you add Herceptin to their chemotherapy regimen you get much greater efficacy, a higher response rate, and most importantly longer survival. So this study that showed this really is practice changing. We are now recommending that all patients with metastatic gastric cancer have their tumor tested in the pathology lab for the presence of this protein HER2/neu and if that test is positive, we are recommending that those patients should receive Herceptin, this targeted antibody, in combination with chemotherapy as a part of their treatment. Now, I would add that Herceptin of course has been FDA approved in breast cancer for many, many years. It's not yet FDA approved in gastric cancer, but we expect that, and hope that it will be within the year. Fortunately we were able to get approval to use the drug in patients who are testing positive for this protein HER2/neu. So this has been a very important and exciting breakthrough in the field.Foss Is it now standard practice to test all tumors for HER2? Lacy It is evolving, and this is relatively new, so people are just beginning to incorporate this into their practice, but yes, pathologists are on alert and they are now beginning to do this routinely.Foss There was another really exciting advance that was actually reported this year at the American Society of Clinical Oncology, and that involved the use of the drug Avastin, which is an antiangiogenic factors in gastric cancer.Lacy Avastin has

been a very exciting antibody, a targeted therapy, which was approved about 6 years ago now in metastatic colon cancer and it was an enormous breakthrough in the field. The study showed that Avastin in combination with chemotherapy in colon cancer improves the efficacy of chemotherapy and again, extends survival. Since that time, Avastin has also been approved for use in combination with chemotherapy in lung cancer and in breast cancer and more recently it has been approved also in brain tumors and kidney cancer, so this has been really a Blockbuster drug in the field. We think it works by interfering with blood flow to the tumor and what is very exciting is that this year, two weeks ago, at the National Cancer Meeting in Chicago, the data was presented from a large clinical trial in gastric cancer. This trial was conducted largely in Asia and Europe, to a lesser extent in the United States, and the patients were given either chemotherapy alone or chemotherapy with Avastin and what the study showed was that again Avastin improved the efficacy of chemotherapy, the response rates were higher, and the time to progression of disease was higher and the survival was also better by about two months, although it was not quite statistically significant. What was also quite interesting is that when they looked just specifically at the American patient population, the benefits of Avastin seemed to be much more dramatic with an increase in survival of about four months, which is very impressive. There was a lot of buzz at the meetings about Avastin and gastric cancer. We will certainly be seeing more studies with Avastin. We actually have a clinical trial open here at Yale for patients with metastatic gastric cancer with chemotherapy and Avastin and I think this is going to be an ongoing and exciting story in the field. Foss Jill, it sounds like a lot has changed over the last 10 years or so in the treatment and management of gastric cancer. Lacy It has, and thank you Francine. Foss It has been really great to have you here as our guest today on Yale Cancer Center Answers to talk about new advances in gastric cancer. Until next week, this is Dr. Francine Foss from Yale Cancer Center wishing you a safe and healthy week. If you have questions or would like to share your comments, visit 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 on the Connecticut Public Broadcasting Network.