Drs. Daniel Boffa and Jill Lacy, Treatment Innovations for Esophageal Cancer July 5, 2009Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening Ed and Francine are joined by Dr. Daniel Boffa, Assistant Professor of Thoracic Surgery, and Dr. Jill Lacy, Associate Professor of Medical Oncology. Both Dr. Boffa and Dr. Lacy are experts in the treatment of esophageal cancer.Chu Let's start off by defining for our listeners what is esophageal cancer?Boffa Esophageal cancer is an abnormal growth of the cells that line the esophagus. The esophagus is the swallowing tube that starts at the back of your mouth and goes through your chest and into your abdomen where it connects your intestine with your stomach. The cancer is a loss of the ability of a cell to control its own growth, so not only does that cell grow out of control, it loses its borders within the neighboring cells and not only grows through the tissues of the esophagus, but can enter the blood stream and spread throughout the body.Foss Jill, esophageal cancer is one of the fastest rising cancers in the United States. Can you talk a little bit about what causes it and what the incidence is in the United States?Lacy This dramatic increase in the incidence of esophagus cancer is due to an increase in one type of esophagus cancer called adenocarcinoma. Since 1975, the annual incidence of adenocarcinoma in the United States has increased by a dramatic 400% and this was at a time when the incidence of the second major type of esophagus cancer, called squamous cell carcinoma, had been decreasing. What's behind this has been referred to as an epidemic of adenocarcinoma of the esophagus, but the reality is that we really don't know for sure. We think it may be related in part to a rising prevalence of acid reflux disease. We do know that long-standing chronic reflux of stomach acid up into the esophagus can cause precancerous changes in the lining of the esophagus, something called Barrett's esophagus. And Barrett's, we do know, is a very significant risk factor for ultimately developing adenocarcinoma of the esophagus. We also think that obesity may be at play here as well. There is very strong epidemiologic data that links obesity and an increased body mass index to an increased incidence of esophagus cancer, as well as a number of other cancers. There are still many unanswered questions about why we have had this dramatic increase in incidence of adenocarcinoma of the esophagus.3:15 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-05-09.mp3Foss Dan, can you tell us how many cases there are of this in the United States and what age groups are primarily affected?Boffa There were about 16,000 new cases last year in the United States. The majority of patients are in their seventh or eighth decades, so in their seventies, late sixties, through their late seventies, but that being said, all ages, all adult ages, can be affected by this. We see this in patients in their thirties as well as patients in their eighties.Chu Jill,

can you go through some of the main risk factors for developing esophageal cancer?Lacy There are a number of factors that have been clearly identified that increase the risk of developing esophagus cancer, and these risk factors actually differ significantly between the two major types that I have referred to; adenocarcinoma and squamous cell carcinoma. For squamous cell carcinomas of the esophagus there are two major risk factors, tobacco use and alcohol consumption, and each of these independently increases the risk of squamous cell carcinoma, and when used together, the risk is actually significantly amplified. The patients or individuals who are at highest risk of developing squamous cell carcinoma are individuals that are cigarette smokers and smoke heavily, and also heavy drinkers of hard liquor. Their risk is about 100 fold over the general population. Some of the other risk factors associated with squamous cell carcinoma include poverty, malnutrition, diets low in fresh fruits and vegetables, or certain vitamins and minerals. Now, the story is different for adenocarcinoma. There, the major risk factors are long-standing acid reflux disease, or GERD, and it is linked to Barrett's esophagus and Barrett's is really the major risk factor for adenocarcinoma. Obesity also is a risk factor as I had mentioned. Tobacco is only a moderate risk factor for adenocarcinoma and it increases risk by about two to three fold. Alcohol does not appear to be a risk factor at all for adenocarcinoma in contrast to squamous cell carcinoma. In fact, there is recent data that suggests that drinking wine may actually have a protective effect on the development of adenocarcinoma, although certainly that needs to be validated and would not be considered a reason to go out and start consuming wine.Foss Barrett's esophagus is a term that we have heard is a risk factor, and I believe that's primarily a surgical issue, so something that you would address, can you talk about it and what to do about it if you have it?Boffa Barrett's esophagus is the body's response to seeing conditions that it wasn't designed for. The body was meant to propel food in a one-way direction, and that's forward. When patient's get reflux disease, the esophagus is exposed to things from the stomach that it wasn't designed to see, specifically acid as well as some bile acids, and in response to this, the esophagus is injured and tries to protect itself by reverting to a type of lining that looks6:43 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-05-09.mp3 like the intestine downstream of the stomach that normally sees the gastric acid all the time, and that sounds like a good idea. Unfortunately, once it converts into this intestinal-type lining, it loses control over its ability to regulate its growth and overtime that Barrett's can actually be transformed into something called dysplasia, where Barrett's is a metaplasia, which is a stage change to a different kind of lining. Dysplasia is a change to a more irregular, less controlled lining, and that's what's really at risk of converting into a cancer. If you have Barrett's esophagus, we really don't know exactly the best way to treat you for Barrett's. It is more of a marker of a potential to form a cancer. If you took everybody that has Barrett's esophagus, that group is more likely to have cancer, but it's on the order of about half a percent per year. You don't need to rush off and have your esophagus removed just because you have Barrett's.Chu Dan, what would the symptoms be that would

typically be associated with say someone who has developed, or is beginning to develop Barrett's esophagus?Boffa Patients who have frequent heartburn who are on acid suppressive medicines like Zantac and Pepcid are at risk to develop this Barrett's because they are having things reflux into their esophagus and are at risk to develop this metaplasia. About 14% of all patients who have significant reflux that are taking daily acid suppressive medicines will develop Barrett's. On the other hand, 20% of patients with Barrett's have no symptoms at all. If you do have symptoms of gastroesophageal reflux disease and you are taking acid suppressive therapy, it is reasonable to have an upper endoscopy at some point to assess whether or not you have this change. It's something that you can actually see when you do an upper endoscopy, it's a microscopic change that leads to a different appearance of the lining, so just by looking at it you can tell if somebody has Barrett's. If you do have it, then you need to be followed more closely because you are at an increased risk for esophageal cancer.Foss If you get scoped and you don't have Barrett's, and you continue on those acid suppressing medications, can you be reassured that you won't develop Barrett's, or do you need to be scoped on a frequent basis to prevent that?Boffa That we don't know. We have ways of sort of categorizing risk, and unfortunately, nobody's risk of esophageal cancer is zero. Having a long-standing reflux disease, we don't know exactly how much reflux you need to have before you develop Barrett's. I would say that if you have a negative upper endoscopy, that is reassuring, but if you continue to have long-standing reflux disease getting a follow-up upper endoscopy five to ten years later is probably a reasonable thing to do. Unfortunately, we don't have enough information to give hard and fast guidelines, but you should definitely be in contact with the gastroenterologist if10:20 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-05-09.mp3 you do have gastroesophageal reflux type symptoms, even if you have had one negative upper endoscopy.Chu Jill, once esophageal cancer develops, what are the typical symptoms associated with that, is it similar to say the symptoms associated with Barrett's esophagus?Lacy Well there is some overlap. The overwhelming majority of patient's, about 75% with esophagus cancer will present to their physician with the complaint of food getting stuck and difficulty swallowing, what we call dysphagia, and that is usually progressive over a few weeks to in some cases months. It can be associated with weight loss due to decreased intake of food in about 50% to 60% of patient's, and significant or dramatic weight loss is an adverse prognostic factor in terms of outcome. Only about 20% of patient's actually complain of pain when they swallow, what we call odynophagia, and we have been talking about acid reflux. About 20% to 30% of patient's will give a history of long-standing, and in many cases severe, acid reflux. Rarely, patients will present with more advanced disease with a cough, difficulty breathing, hoarseness, and recurrent pneumonias, but that's much less common. I would emphasize that, and this has already been emphasized by Dan, that acid reflux is extremely common in our population and so, just by virtue of having acid reflux it doesn't mean that you are going to, or ever will get esophageal cancer, and similarly dysphagia, although it certainly needs

to be evaluated, it can be caused by a number of benign conditions as well.Foss Jill, as you were talking, it occurred to me that a lot of these symptoms are things that many people have. How often do you see somebody coming in very late, who has had these symptoms and kind of chalked them up to something else?Lacy It certainly happens, I think most patients when they are having difficulty swallowing, and food is hanging up, will consult with their physician within a reasonable period of time.Chu And if any of these symptoms should pop up, who should the individual seek attention from first, should it be their primary care physician, should it be you or Dan, the surgeon, a medical oncologist? Can you take us through the process of who these individuals should see?Lacy If someone is noticing for the first time difficulty swallowing or severe acid reflux symptoms, they probably should start with their primary care physician and undergo an evaluation there, and then he or she can make appropriate referrals to a gastroenterologist and go from there.13:18 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-05-09.mp3Boffa If you are having difficulty swallowing, I think that you really need to have an upper endoscopy or barium swallow, and in general most general practitioners are very aggressive at pursuing the diagnosis of esophageal cancer. However, if somebody is with their primary care physician and doesn't feel that it is progressing, then they should feel free to contact a gastroenterologist themselves or a surgeon themselves.Foss Thank you for that Dan. We are going to take a break now. You are listening to Yale Cancer Center Answers and we have Dr. Dan Boffa and Dr. Jill Lacy discussing the treatment of esophageal cancer.Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu, and Dr. Dan Boffa and Dr. Jill Lacy, experts in esophageal cancer from Yale Cancer Center. Dan, we talked a little bit about the risk factors for esophageal cancer and Barrett's esophagus. Can you tell us how esophageal cancer is diagnosed?Boffa Esophageal cancer is diagnosed by a biopsy and it's performed during an upper endoscopy. One of the themes that we will try to convey to you is the importance of being cared for by a center that has experience with esophageal cancer. The condition we have mentioned before of Barrett's esophagus has a tendency to convert to something called dysplasia, which can either be low or high grade dysplasia, and that just reflects the degree to which the cells have become abnormal, it can look very much like a cancer and the diagnosis can be difficult to establish. At Yale we have pathologists who are specialized in reviewing esophageal cancer cases and its important that more than one pathologist examines a biopsy to establish the diagnosis of cancer.16:22 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-05-09.mp3Chu Jill, once the diagnosis of esophageal cancer is made, what goes into the evaluation process to determine whether or not the cancer is localized or perhaps more advanced?Lacy Once we have a diagnosis, its important to stage the patient and that means determining how big the tumor is and whether it's spread to any other sites in the body. Staging is very important as it determines our treatment and it also determines prognosis. Staging for esophageal cancer

is based on three aspects of the disease, one is how deeply the tumor in the esophagus actually penetrates into the wall of the esophagus, the second component is whether the tumor has spread to the surrounding lymph glands or lymph nodes in the region of the esophagus, and then the third component is whether the tumor has spread to distant sites in the body such as the liver, lungs, or bones, and from those three components we use a 4-tiered staging system, as we do in many solid tumors, going from stage I to stage IV. Stage I would be a very superficial tumor in the lining of the esophagus that's not actually penetrated in to the muscular wall of the esophagus. At the other end of the spectrum, we have stage IV disease, and in that situation the tumor has spread to distant sites in the body, again, such as the liver, and then stage II and III disease, means you may have a tumor that has invaded deeply into the wall of the esophagus or has spread to the lymph nodes or lymph glands in the region of the esophagus.Foss At the time of diagnosis Jill, what percentage of patient's have early stage versus advanced stage?Lacy The majority of patient's present with either stage II or III disease.Boffa What's unusual about esophageal cancer, is it relates to the anatomy of the esophagus, it is a muscular tube, but the lining is more like the layers of a cake and the esophageal cancer starts on the inside, or the frosting of the cake, if you will. What's unusual about the esophagus is the lymph ducts, which allow the cancer to spread, are actually very close to the inside, or very close to the frosting to stick with that tasty analogy, which means that a relatively early stage esophageal cancer has much readier access to spread then say a colon cancer or breast cancer. If you compare stage per stage, esophageal cancer is a very difficult cancer to manage because of that anatomic reason, it has an earlier propensity to spread.Foss So, it would be very rare to pick up a stage I case for instance?Boffa Historically yes, but now we are doing screening programs. Once it is established that you have Barrett's esophagus, if you are followed, chances are you will be much more likely to be found to have an earlier cancer or even high-grade dysplasia then the more symptom driven diagnosis, which tends to be the stage III cancers.19:45 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-05-09.mp3Chu Dan, can you take us through some of the different treatment options, in particular the surgical treatment options for this disease.Boffa Esophageal cancer can be treated with chemotherapy, radiation and surgery primarily. We have other techniques, but if you had to separate the treatment for esophageal cancer, there is treating the tumor in the esophagus with local therapy, which means you are trying to get rid of the tumor where it started, and there is systemic therapy, which means you are treating the whole patient for anything that may have spread; systemic therapy is chemotherapy. Local therapy can either be radiation where you try to destroy the tumor by radiating the esophagus and neighboring structures, and surgery is where you remove that part of the esophagus and all of the tissue around it. Esophageal cancer, again because of where it is in the body and the extent of surgery you have to do to restore the patient's ability to swallow normally, is a difficult cancer to treat surgically. It involves a substantial operation. We select our patients very carefully because the risk of esophageal surgery is much

higher then say colon surgery or breast surgery. At Yale, every patient is evaluated individually, and if we think there is a risk of them having cancer throughout their body, even if it's microscopic and you can't see it, we give them chemotherapy. Most patients get treated with chemotherapy and radiation followed by surgery, sort of a multimodality approach, and the thought behind that is that we give patients everything we have because it is a difficult cancer to control both where we see it and where we don't.Foss Jill, can you talk a little bit about the kinds of chemotherapy that are used for esophageal cancer?Lacy As Dan has alluded to, the management of esophageal cancer is typically interdisciplinary; it involves the use of radiation, chemotherapy and surgery. Chemotherapy has an important role to play in the management of all stages of esophageal cancer with the exception of stage I, which is typically handled with either surgery or focal ablative therapies. There are two major scenarios where chemotherapy is important. First, in a situation where you have a patient and they do not appear to have metastatic disease and the plan is to take them to surgery for localized or regional disease, and there, as Dan mentioned, we use chemotherapy in combination with radiation that's administered prior to surgery. This will reduce the size of the tumor and hopefully eradicate any metastatic disease. This approach has been shown to increase the cure rate overall compared to surgery alone. The most commonly used and established regimen that we use with radiation is a two-drug regimen using older drugs, cisplatin and 5-fluorouracil, and they appear to still be the best regimen that we have. We also use chemotherapy, again in combination with radiation, in a patient who may not have metastatic disease but is not a candidate for surgery because of medical problems that would23:26 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-05-09.mp3 make the risk of surgery too great. In that situation we know that chemotherapy, again when given with radiation therapy, concurrently not only can shrink the tumor substantially and improve symptoms, but also in about 20% of the patients it actually appears to be curative in the long run.Chu Jill, is there ever any role for giving chemotherapy after the surgical procedure has been performed to remove the esophageal cancer?Lacy Yes, there are some situations where going in to surgery all of the staging studies would support an early stage esophageal cancer, say stage I, and then once the esophagus and all the lymph nodes are removed we find that the stage is actually higher than that, stage II or III, and that's a situation where we know the patient is at significant risk for recurrent disease and we certainly would consider using either chemotherapy alone, or in some cases, depending on the location, chemotherapy and radiation therapy in hopes of reducing the risks.Foss Jill, what is the role of some of the newer biological therapies such as bevacizumab, which is the anti-angiogenesis antibody in the treatment of esophageal cancer?Lacy Unfortunately, more than 50% of patients with esophagus cancer, even best case scenario, will have a recurrence or will present with metastatic disease. In that setting, we don't, at the present moment, have definitive curative treatments. We know that chemotherapy has an important role to play here; chemotherapy can often dramatically shrink the tumor, thereby improving symptoms such as difficulty

swallowing and improved quality of life and can also significantly extend survival. But chemotherapy over many decades has not been proven to be curative in this situation. So certainly we are searching and looking for better therapies and there is tremendous interest in these new so called targeted or biologic therapies, and one such targeted therapy that looks very promising for adenocarcinoma of the esophagus is Avastin or bevacizumab. This is a targeted therapy that's received a lot of media attention. It is a blood vessel formation inhibitor, so we think it may work by blocking blood supply to tumors, and it's already been approved by the FDA for common cancers such as colon, breast, lung, and just last week in malignant brain tumors. We think that it may also be an active agent in adenocarcinomas of the esophagus. We have an ongoing study here at Yale using Avastin, or bevacizumab, in combination with the chemotherapy regimen in patients with adenocarcinoma of the esophagus, and also stomach, who have either recurrent disease after initial definitive treatment or present with metastatic disease.Chu Great. Dan, over the last few years there has been an increased use of giving chemotherapy before surgery, and I'm just curious, from your perspective as a surgeon, have you noticed26:47 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-05-09.mp3 any increased complications resulting from chemotherapy beforehand, or have you found it to be much more helpful in allowing you to get in there and surgically remove the tumor?Boffa Well, it's a very big operation and I can say that the chemotherapy or radiation beforehand doesn't seem to significantly alter the chances of having a complication. Now that being said, complications are common after esophagectomy and complications that are well managed don't really affect the long-term outcome. What the centers that do esophagectomies with frequency have over centers that don't is their ability to identify complications and manage them safely so that the overall result is very good. Centers like Yale that see a lot of esophageal cancer and do a lot of esophageal operations have a real advantage over centers that don't and are able to conduct these elaborate procedures very safely.Foss We talk about multimodality care for many cancers and both of you alluded to the multimodality approach for esophageal cancer. For most patients who present with this, how did they enter this system? How did they hook up with multimodality care?Boffa As it's set up right now, if any of the members of the multidisciplinary team, be it Harry Aslanian through gastroenterology, Jill, or myself, once you are referred to any member of the esophageal cancer team you become cared for by the team. You still are cared for by the physician that referred you, but you are discussed at the tumor board and we come up with a consensus care plan to move forward.Chu Great, well Jill and Dan thanks so much for being with us on the show this evening. We look forward to having you back on a future show to hear the latest about what's going on in the treatment of esophageal and gastroesophageal cancer. You have been listening to Yale Cancer Center Answers and we would like to thank our guests, Dr. Dan Buffa and Dr. Jill Lacy for joining us this evening. Until next time, I am Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.If you have questions or would like to share your comments, go

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