Dr. Charles Cha, New Hope for Advanced Colorectal Cancer June 22, 2008Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller is a medical oncologist specializing in pain and palliative care, and he serves as the Director of the Connecticut Challenge Survivorship Clinic. 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 Ken Miller welcomes Dr. Charles Cha. Dr. Cha is Assistant Professor of Surgery specializing in gastrointestinal cancers at Yale School of Medicine.Miller Dr. Cha, today we are focusing on the upper GI cancers. What part of the body is that?Cha Upper GI cancers involve cancers of the liver, bile duct, pancreas, stomach and esophagus. It combines a whole lot of different categories of different types of tumors. My particular expertise is in that of colorectal cancer, particularly colorectal cancer that has metastasized to the liver, and the different therapies available, in particular, surgical therapy and the new exciting technologies and techniques that we are able to do now for patients with this disease process.Miller Typically people who are listening will say that a cancer that goes to the liver is very bad. What has changed in the last 10 years?Cha As you mentioned, historically the outcome for patients with stage IV disease for any type of cancer, including colorectal cancer, is quite poor. However, in the past decade or so there have been dramatic changes in our treatment of these patients. In particular, the combination of newer chemotherapeutic agents to wipe up microscopic disease, and surgical technique and technology in terms of being able to remove a disease that is metastatic to the liver, to the lung, even to local areas around the original site. We were able to go from a situation where previously a patient with stage IV disease really had no foreseeable long-term survival, to the point where with liver metastases we now have reports where patients can live anywhere up to 60% to 70% five-year survivals following liver resection if we can completely get the tumor out. We are getting fairly aggressive in terms of who we consider candidates for surgical resection.Miller For example, if someone has colon cancer and you find out a year later that there is a single metastasis in the liver, what would be the approach to taking care of that patient?Cha It is always going to be a two-hit approach and that is why we keep using this multimodality therapy as a keyword in terms of what we do. We3:02into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3 work very closely with the medical oncologist in terms of treating those patients with chemotherapy. A lot of times we do it upfront and a lot of times we do it after surgery. That is individualized amongst patients, but we are tending to give a lot more patients 3 months of chemotherapy first, sending them for surgical resection later. We will do that even for patients who have something that we would consider unresectable disease, because we can convert a certain number of patients from an unresectable situation to a situation where they become respectable. I had a patient just recently who had 15 metastases to the liver and we were able to convert him to a resectable situation. We did a laparoscopic liver resection on one side, we can talk about some other different

techniques, and we embolized his portal vein on the other side to allow the residual liver to grow. We are going to go back in a few more weeks and resect the other side, so we are doing a sort of stage bilateral resection. Part of the ability of this, is the remarkable ability of the liver to regenerate. I can remove up to 80% of the liver in any one setting, and within a week it will grow back in volume, and in 2 weeks in function. It gives us a lot of leeway to be able to remove a lot of the liver as long as we can preserve a necessary blood flow and structures that go to that section.Miller It is incredible listening to that. I have been an oncologist many years and I actually didn't realize how quickly the liver regrows.Cha It is quite impressive, and on top of that the fact that 2 decades ago the mortality following liver resection was quite high, almost 25%, so one in four were dying.Miller Now in comparison what would we have?Cha Now in modern times, it is less than 5%, but in large centers it is close to 0% mortality. That is improvement in surgical technique, but also improvement in ICU care, in terms of anesthesia care. There are a lot of things that have flown in conjunction with that, and it has allowed us to be fairly aggressive in terms of removing lesions.Miller Someone who has a single liver metastasis, it sounds like they would probably get chemotherapy at some point in their care and they will hopefully have surgery. You just mentioned the patient with 15 metastases.Cha That is right.Miller Does that person have a chance of being cured of the disease?5:29into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3 Cha Certainly, 10 years ago the thinking was that if you had 3 or more lesions, if you had a larger lesion or if you were of older age, that you were not a candidate for resection. Those criteria have changed in the past 5 years. As I mentioned, if I can preserve just 20% of the healthy liver and get all the lesions out, there is good data to support the fact that you will have long-term survival; 5-year survival even in somebody with 15 liver lesions is around the 30% range. We can get a certain percentage of those patients to 10 year survival, probably not as high a percentage, but once you reach the 10-year mark we have good data to show that those patients are essentially cured of their disease. We shoot for long-term survival, we shoot for cure, but as with a lot of different disease processes we're converting the thinking from cure to not cure, to converting patients to a chronic disease. Some of these patients will have recurrences in the liver or other areas of body that we can then deal with, but it is a lifelong battle. Along the way we partner up with patients in terms of understanding what we are going into, that we can extend their life significantly and not affect their quality of life during that time period.Miller Let me ask about some of the advances in surgery, in particular, lets talk a bit about laparoscopic surgery. The laparoscope is used for gallbladder surgery or for appendix, how do you use it in terms of treating liver metastases?Cha I approach laparoscopic liver resections almost the same way that I would approach an open liver resection. We start out by putting small keyhole incisions in the abdomen. Often times we do need to make a larger incision to be able to get the tumor out eventually, but we start out by looking at the entire liver with an intraoperative ultrasound with

special laparoscopic probes. I can see lesions as small as 2 to 3 mm using that type of technique, which is better imaging than any other preoperative imaging that we have. Then, based on that, I can determine whether or not we can remove this laparoscopically and if we can, then we would proceed in a very similar fashion to remove it.Miller Let me ask you further about the imaging, the patient is now having PET scans and CAT scans and MRIs, the ultrasound that you do at the time of surgery is better than those?Cha It actually is better than those techniques; however, there have been a lot of advances in terms of preoperative imaging and CAT scans and MRIs and PET scans that clearly pushes in the right direction towards resection. We can tell with about 90% reliability that we are going to be able to resect by preoperative imaging. The intraoperative ultrasound will allow us to change our management or change what we do about a third of the8:42into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3 time. It is very useful and most of the time it does not mean that someone is going to become unresectable, it just means we are going to remove one more lesion or ablate a lesion that we cannot remove, or do something different than we had originally planned, so it is very helpful.Miller I used to hear some of my surgical colleagues say that there is nothing that replaces feeling with your hands when you operate, is that true now?Cha Those times are changing as people become more comfortable with laparoscopic surgery. I feel just as comfortable doing things laparoscopically as not. Sometimes, if necessary, and because we are making an incision big enough to take the tumor out, we do use a hand port where I put one hand in and that is more of a safety issue. The liver is quite vascular and if there is bleeding, I can control things a little bit quicker and better that way, but often times, we will do it completely laparoscopically. That has to do a little bit with the comfort level with laparoscopic resections. The recovery time is a lot quicker. The patient experiences a lot less pain. In one recent patient that had 15 liver lesions, we were able to do rectal resection laparoscopically combined with a liver resection at that same time period, and the patient went home in 6 days postoperatively. I do not think that would have been as quick a recovery had we not done it laparoscopically, so I think it does pose significant advantages.Miller In terms of some other techniques, you mentioned when you are operating sometimes you are actually removing a lesion, and you also mentioned other techniques that you have for eliminating a lesion in the liver, perhaps without removing it. What are some of those?Cha There are a number of different ablative procedures that you can do for liver lesions as well. There is radiofrequency ablation, which essentially is putting an electrode into the liver that will heat up the liver and essentially necrose, or cook, that portion of the liver. There is also cryoablation where you put a probe in and use Argon gas to cool the tumor down to a temperature where it will freeze. There is also a newer technology, microwave technology, where you put a microwave probe in. Essentially, all these technologies are great supplements to surgery, but none of them work as well as surgically removing them, and that has been demonstrated in a number of different trials showing that the recurrence rate following this ablative procedure is a higher local

recurrence rate than when removed surgically. For metastatic colorectal cancer we do mostly surgical resections and we know that even a wedge resection is better than ablating a lesion. In certain situations, where we cannot completely remove all lesions, we will ablate, but it is quite rare now-a-days for11:39into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3 metastatic colorectal cancer to do that. For primary liver cancer, such as hepatocellular cancer, we do quite a bit of ablation, mostly because a lot of those patients do not have a liver reserve, because of cirrhosis, to tolerate liver resection.Miller It sounds like for a lot of the other patients who have a healthy liver, other than the cancer, that you are able to remove a large amount of cancer and then the normal liver grows back.Cha Absolutely, like I said, as long as we can get around 20% to 25% residual liver, that liver will grow back just fine. Sometimes patients will experience a temporary period where they have some difficulty with their liver regenerating, but typically we can get them through that initial period and they should have no change in function of the liver.Miller Are there any ideas or theories about why the liver can regenerate and not other organs?Cha It is a good question and something that a lot of research is going to try and resolve. It is not really known. We do know that unlike other types of cells, hepatocytes have the ability to regenerate at the cellular level, about 30 to 40 times, so that is why patients can become cirrhotic if they damage the liver enough times, such that each individual liver cell has died off about 30 or 40 times, and at that point you just get fibrosis, but in a healthy liver, when you resect, there are some mechanisms that turns on. Whether this is angiogenic factors or certain cytokinins that influence the cells, and some people think that those cytokinins are produced by the gut that flows through the liver and allows some signal to be turned on for the liver to increase in size until it is able to turn off that signal from the gut.Miller If you looked at someone's liver who has had a liver resection, and a liver as large as say 75% grew back, would it look like the original liver?Cha We talked about regeneration, but what this really is, is hypertrophy of the residual liver. The volume grows back to the original size, but you do not get new blood vessels and you do not recreate that portion, so it is actually more the residual liver that then hypertrophies in size. It does look like the original liver in size, but it is really the residual liver that has grown back to the original volume. Certainly it is normal liver tissue again, and like I said, when we do bilateral liver resections we will do the stage resections to allow the residual liver to grow back to its regular volume so that we can go ahead and take more of the liver. The other technique that we use to help increase the amount of residual liver is portal vein embolization.14:28into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3 Miller Let me ask you a little bit more about that because there are mainly two blood supplies to the liver. Can you tell us a little bit about that and why you choose the portal vein to tie off the blood supply?Cha Well it is sort of a matter of trial and error. As you say, there are two main blood supplies, the hepatic artery and the portal vein. The portal vein is blood that is coming from your gut that is flowing to the liver to be detoxified before it goes into the regular venous

system. We have noticed that if we can ligate the portal vein, there is still plenty of blood flow through the hepatic artery to keep the liver alive and to cause not too much discomfort. The side that we ligate will then shrink in size and allow the other side to hypertrophy just as if we had done a resection. In somebody who has a liver residual that is going to be less than 20%, we can then ligate the opposite side and allow that area to grow so that the future liver remnant, once we remove that portion of liver, will be an additional 10% to 15 % larger in size. The gentleman that we talked about earlier, I did a laparoscopic embolization of the portal vein on that side as well as laparoscopically. It is also typically done percutaneously so that the interventional radiologist can go in and put a catheter into the portal vein and put special embolic particles to stop the blood flow on that side.Miller We would like to remind you to e-mail your questions to www.canceranswers@yale.edu. Weare going to take a short break for a medical minute. Please stay tuned to learn more information about gastrointestinal cancers and about liver surgery with Dr. Charles Cha from the Yale Cancer Center.Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and I am here with Dr. Charles Cha from the Yale School of Medicine discussing some of the latest research on liver surgery and on gastrointestinal cancers. I want to take this opportunity to learn more17:25into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3about nanoparticles, as I know you are involved with this. What are nanoparticles?Cha That is sort of the catchword of the day right now, but it is pretty exciting research that we are doing. My laboratory in particular is looking at ways of cutting off the blood supply to tumors as they grow, because we know that without additional blood supply, tumors cannot grow any larger than a couple of millimeters in size. It is a technique that has been popularized and it is known as angiogenesis. We are using a nanoparticle delivery system right now in animal models to package special molecules that will directly impede the ability of RNA molecules to correct the angiogenic factors that are necessary to cause this blood flow influx to the tumor cells. That is simplified a bit, but it is really just nano particles that can be injected and then specifically target angiogenic factors in tumors and shut down the growth of the blood supply to those tumors. It is really an exciting area of research for us right now and we are making dramatic strides in seeing the reduction in tumor growth both in animal models and cell models and it is something that we hope to eventually translate to a human model as well.Miller When I hear the word particle, I actually picture a particle. Are they physical particles, how big are they and how have you modified them so that they are essentially like a Trojan horse?Cha They are physical particles. It is a lipid-based particle in conjunction with other polymers, essentially, and we can package whatever the gene target that we are trying to shut down within that particle is. It then goes into the system and dissolves once it reaches the target. We can coat those particles with antibodies as well to try to specifically target areas, allow them to dissolve, and once the delivery system has dissolved the sRNA or the RNA, that will cause the angiogenic factors to shut down and will then specifically target the angiogenic molecules.Miller For

example, we have the drug now called bevacizumab, or Avastin, which is given intravenously. The purpose is to turn off angiogenesis, or the creation of blood vessels, but you are saying in a sense that you are delivering a gene therapy, or a therapy that actually acts on RNA and DNA directly to the target, which are the cancer cells.Cha That is right. The original results with bevacizumab were exciting, but there was not quite as big a change in terms of survival that we were originally hoping for. We're sort of attacking that on 2 different levels. One, as you mentioned, is targeting the tumor directly using these nanoparticles to deliver the angiogenic factors, as well as targeting the20:51into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3 sRNA. It is a little complex, but the mRNA is the message that then gets translated into the actual vascular endothelial growth factor of the protein that bevacizumab will then try to block. It is a different, earlier stage in the growth or the development of this VEGF which bevacizumab targets. We are hoping it works like stopping a plant from growing when it is still a bud, how it is more effective than trying to chop the weed off at the top. That is the approach that we are taking, targeting VEGF at an earlier stage in its production rather than trying to just block it from doing the bad things that we know that it does.Miller It is a fascinating concept. Would this therapy work better if you added bevacizumab, a drug that acts on the fully developed weed or the plant as opposed to the bud?Cha Absolutely, that would be our stage 3 or 4 approach. The next question will be, will this work in conjunction with standard chemotherapeutic agents? These are all the things that we are looking at currently in the lab.Miller You are running a laboratory now. What are some of the other research projects you are working on?Cha There are a number of different clinical trials going on and most of them are being run by medical oncologists. From my perspective what we are looking at in terms of technology is expanding the patient population that we perform these laparoscopic liver resections on and being innovative in our approach in terms of the portal vein embolizations laparoscopically and who we consider for surgical resection. We are pushing the limits a little in terms of extrahepatic metastases as well. We know that resecting lung lesions still result in a 5-year survival for 60% or 70%. Some clinical centers have trials for debulking colorectal cancer, and that is something that is an area of controversy and something that in very select situations we will consider as part of a clinical trial. Most of the trials that I go around are chemotherapeutic combining some of the neurobiologic agents such as bevacizumab and some of the anti-EGFR agents such as cetuximab and panitumumab; those sorts of agents, in combination with standard chemotherapy, to sort of tweak things so we were getting even a better response.Miller Let me ask about the multidisciplinary nature of your work. When a patient comes to Yale, or another major center, who is part of the team and who sees the patient?Cha The majority of our patients get reviewed at multidisciplinary tumor boards. That is something that is essential because the medical oncologist24:14 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3 does not know exactly what I consider resectable and unresectable and I do

not have a complete full understanding of what the indications for the different biologic agents are and what the issues are in terms of toxicities with some of the chemotherapeutic agents. I will try to learn as much as I can. We have a radiologist specific for our disease processes, pathologist, radiation oncologist, which becomes significant for rectal cancer where radiation is used and sometimes for the liver if the things are unresectable. You have the medical oncologist, you have the surgical oncologist, and a number of trainees are also there and we go case-by-case. We show the films in terms of imaging. We show the pathology in terms of the pathologic significances in each expert for each phase of this discussion. Everyone puts in their two cents in terms of what they think is going on and then we come to an overall consensus for what to do for any particular patient. The key to that is that we can individualize for any specific patient based on the available data because the data is large and varied and applies in different ways to any individual patient.Miller Let me ask you about a different topic which we read a lot about, the liver transplant. That is something that has been done at Yale by Dr. Embrey. How is that used in terms of patients with cancer?Cha It has a great role in terms of primary hepatocellular carcinoma, but not really for a metastatic colorectal cancer. Dr. Embrey has done great things at Yale, in particular with the liver transplant program, but for metastatic colorectal cancer transplant is not really indicated. We know that from any stage the immunosuppression that you get when you have a liver transplant causes problems in terms of tumor growth for this particular disease process.Miller It sounds like for a cancer that has spread to the liver it is better to remove those areas than to remove the liver.Cha That is right. A combination of chemotherapy and surgical resection would be the key. We know we can get response rates up to 40% to 50% with some of the biologic agents, but what is well known is that you can't really ever cure anybody unless you surgically resect them. The bulk of the disease needs to be removed surgically and you rely on chemotherapy to make sure that the cancer does not come back.Miller Laparoscopy is one of your tremendous expertises. Is that being used for other upper GI cancers, the stomach or the small intestine?Cha Absolutely, we do a fair amount of laparoscopic surgery for gastric cancers and in particular the GI stromal tumors. For pancreas cancer, we27:23 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-22-08.mp3 are actually almost exclusively doing laparoscopic distal pancreatectomies now-a-days. There are some groups though, not many in the United States, that will attempt laparoscopic ahead of the pancreas, which is a pretty complex operation. It is something that maybe 10 years from now will be the standard of care. It is a field that is rapidly moving and improving. Laparoscopic colons have almost become the norm now that we know the data exists showing that the results, at least for colon cancer, are equivalent to that of open procedures. As time goes on it is becoming more and more the standard of care rather than innovation, I would say.Miller It has been very, very exciting hearing about this, especially as a non-surgeon. I have learned a lot today. Charles, I want to thank you for joining us on Yale Cancer

Center Answers.Cha It was my pleasure, thank you for having me.Miller It has been a great program. Until next week, this is Dr. Ken Miller and I want to wish you, from the Yale Cancer Center, a safe and healthy week.If you have questions, comments, or would like to subscribe to our Podcast, go to www.yalecancercenter.org where you will also find transcripts of past broadcasts in written form.