Dr. Harriet Kluger and Dr. Edward Uchio, Innovations in Kidney Cancer July 13 , 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 also 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 we look at kidney cancer. Ken Miller welcomes Dr. Harriet Kluger and Edward Uchio. Dr. Kluger is Assistant Professor of Oncology at Yale Cancer Center and Dr. Uchio is Chief of the Urology Service and Director of Urologic Oncology at The VA Connecticut Health Care System.Miller Harriet, let's start talking about what causes kidney cancer and why the incidence seems to be increasing.Uchio The issue is that, before, patients would come with symptomatic disease and over half of them would come with metastatic disease. Now, with the administration of CAT scan and ultrasound, we are picking up a lot of asymptomatic tumors. If you look at the data, over half of these tumors are presenting asymptomatically so they have come in for some other reason, maybe some GI upset, and a majority of these patients are getting scanned in the emergency room so we are seeing much smaller tumors, but the incidence has jumped significantly in the past few years.Miller Are there patients where the cancer is being diagnosed because of the CAT scan where perhaps it never would have become evident?Uchio Absolutely, and I think that the problem is that we are treating it like we used to treat it when they would come in with significant sizes; we would perform surgery for these and have no problem. Now, we are seeing small tumors in the 1-cm range, and beyond even the definition of the CAT scan itself. We know that there is a lesion there, and now we have to follow them with CAT scans. So there is a significant population, especially in our clinics, that we are following and we are not doing anything for them.Miller Is it your sense that the incidence of it is increasing? Is there something in the environment such as cell phones?Kluger The incidence of death is also increasing a little so one can assume that perhaps the true incidence is also increasing, not just the incidence of diagnoses. It is not increasing as rapidly and as dramatically as the actual incidence in diagnosis. We were just talking before that in the reports from 2006 they mentioned 35,000 cases in the United States and in 2007 it went up to just over 50,000. For 2008 the projected incidences are 54,000 and that is a dramatic increase in incidence.2:59into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3Miller It really is.Kluger Whether or not it is true new cases, or just earlier detection and detection of things that in the past would have been missed, we do not really know. But we assume that it is more the detection of things that would have been missed in the past.Miller Is there a difference between kidney cancer and renal cell carcinoma?Kluger Kidney cancer essentially means cancer that arises in the kidney. There is a whole batch of different types of cells in the kidney and one of them is a renal cell, or renal tubular cell. Without getting into too

many technical details, renal carcinoma is a majority of the kidney cancers, but not all of them. You can have lymphoma of the kidney, you can have renal pelvis cancer, and so.Uchio If you look at the literature, everyone uses kidney cancer, and they are basically talking about renal cell carcinoma because that is about 95% of the cancers. Although we are seeing more of these cancers we may not be treating all of them. It is not that they do not need to be treated, but we are seeing them in a lot of different age groups and with some of the age groups their life expectancy is very short and they have significant co-morbidities, and subsequently, observation does become a treatment option.Miller For example, if you find a kidney cancer in a person in their late 80s, might you adopt that kind of watchful waiting approach?Uchio Absolutely, we bring it up because there is some data, especially from the Toronto Group who has followed a significant portion of patients who have had significant co-morbidities, which make us not want to treat them. When you start to bring in new modalities of treatment, we have a different way of treating patients that is not surgery; they do not go under anesthesia. Some people just do not want anything done first of all, but now we can treat things minimally invasively. I usually give everyone an option for treatment.Miller Who develops kidney cancers more, men or women? Are there certain ages or certain parts of the country that develop it more?Kluger More men than women and it is more common in African Americans. It is also more common in people with other risk factors which include smoking, obesity, and certain hereditary conditions.5:30into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3Miller I want to get into some of the issues about how you make a diagnosis. If a patient has a CAT scan for some other reason, and you find a small little mass in the kidney, say 1 cm or half an inch, how do you decide if it actually is a cancer and then how do you embark on the treatment plan?Uchio Our main issue is this lesion in the kidney; is it solid or not? A lot of patients have cystic lesions which require no follow-up. The way we find out if it is solid and potentially cancerous is we do a CAT scan and we give IV contrast, but these days even people coming to the emergency room are getting contrast, so we can usually tell by the referral with the CAT scan if this is likely to be a malignant.Miller How do you take it from there in terms of biopsies?Uchio That is a very, very interesting question because with most cancers the mainstay is a needle biopsy. Kidney cancer is a little different here. There is a sampling error when we do biopsies in which you can get normal tissue and maybe did not actually hit the lesion. You definitely wouldn't want to watch a lesion like that. Basic standard of care is to excise the lesion or to take the whole kidney out, and under pathologic examination of the whole kidney or whole lesion, we decide if it is malignant or not. The majority is malignant, but as we start to find these much smaller tumors like we discussed earlier, the malignancy rate is actually decreasing, but it is still around the 80% range.Miller You began to talk a little bit about minimally invasive ways of treating cancer, which you have said is very exciting compared to taking the entire kidney out, can you tell us more about that?Uchio The two main groups are either surgery, or ablation for treatment. Standard surgery

can be done where we make an incision or cut the abdomen or side of the body, or we can do it laparoscopically. That is also called minimally invasive therapy. If you want to look at the most minimally invasive therapy, we are talking about ablation therapies. We do not do those through incisions. At the most invasive, we will do it laparoscopically through little holes in the abdomen, or what I specialized in, which is percutaneous treatment. The majority of treatments I do now are percutaneous, where I put the needle straight through the skin. This is a 17-gauge needle which is very, very small and we do that with minimal local sedation. I do it under the CAT scanner and they can go home the same day with just a Band-Aid on the side of the body.Miller You put a needle right into the tumor and then what?8:31into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3Uchio There are two ways to do it. Once you get the needle in there you could either kill the tumor by heating it, which is called radiofrequency ablation, or you can freeze it, which is called cryotherapy. I do both of them but cryotherapy does have its advantages. You can see the ice ball in the freezing zone much more accurately and so that is my modality of choice.Miller Does that work as well as surgery?Uchio That is where things get a little sticky because the technology is going well beyond what our study has shown. With minimally invasive ablative therapies, we only have intermediate data. We are talking about 3 or 4 years of following these patients and seeing what the treatment rates are, but early on, the intermediate data looks very good. If you look at our protocol that we have, we have a 100% treatment rate where we have no enhancement post-treatment, which is what we call 100% cure.Miller Harriet, we talk about local control for the cancer itself, but I know as a medical oncologist your speciality is on the entire body. What are some of the concerns and risks for people that have had a cancer in the kidney?Kluger When the patient first comes in we do what we called staging. We try to see the extent of the tumor, if it is localized to the kidney or potentially one lymph node, we will resect it all and sometimes it has gone beyond that. If it is metastasized a little we will still perform surgery. After surgery you have patients who have no evidence of disease by any kind of CAT scan, and then you have patients who have measurable disease and they are treated very differently. For the patients who have no evidence of disease, a certain percentage of them will have a recurrence and that percentage depends on how much disease they had in the first place and how aggressive the disease was. In an individual patient we can never say with 100% certainty whether the tumor is going to come back at any point or not. We have a whole batch of different clinical trials for these patients to see if we can decrease the likelihood of the tumor coming back. The other groups of patients are the patients that have measurable disease, whether they had their kidney taken out or not, and those are treated very differently. If there is residual disease, it is not respectable and we have to then treat them with something that is either in IV or pill form so it can go to all different parts of the body; this is also a very, very exciting arena. We started offering this in the 1990s, with our first drug approved by the FDA for kidney cancers called high-dose interleukin-2. There is about a 20% response rate for kidney cancer and some of those responses

end up being cured. Some of the patients that were treated in the 1980s have never had a recurrence. However, from 1995 onwards, we had nothing else to offer the other 80% of patients, and standard, old-fashioned11:36into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3 chemotherapy does not really work for kidney cancer. But right now, we are on the verge of a revolution in the way we treat kidney cancer. Over the last three years, three drugs have been approved by the FDA for kidney cancer; 3 additional drugs and another one is about to be approved. This has changed the way we approach this disease.Miller People say kidney cancer is different than other types of cancer because it has some unusual qualities. What are they and what makes it unique?Uchio It is a very strange tumor that it is not radiosensitive and it is not chemosensitive until these specific inhibitors came out, but what we did see in this tumor group was that some of these patients had regression and their body could fight it and get rid of the tumor, and that is where the big push was for these immunotherapies like interleukin-2. My training was at the National Cancer Institute and a lot of that was with the immunotherapy group. That is why other things such as bone marrow transplants and those sorts of things have always become exciting potential therapies before these types of new drugs that Harriet talked about, these tyrosine kinase inhibitors, were brought to light. In addition, she mentioned that this is a very strange tumor. We actually have a surgical role in metastatic disease. We do take the primary tumor out, and that is not common in most cancers because it has not really been shown to affect the course of the cancer in other diseases, but we have randomized trials that show that it benefits, at least in immunotherapy, so we do take out the primary lesion here.Miller We are going to get back to that in a minute because that is unique and very, very interesting. I would like to remind you that you can e-mail your questions to our experts at canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more information about kidney cancer with Dr. Harriet Kluger and Dr. Edward Uchio.14:22into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3as the Yale Cancer Center to make new treatments, not yet approved by the Food and Drug Administration, available to patients. This has been a medical minute, and you will find more information at www.yalecancercenter.org. You are listening to WNPR health forum from Connecticut Public Radio.Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and today I am joined by Dr. Harriet Kluger and Dr. Edward Uchio. We are talking about the treatment options for people with kidney cancer. Edward, if someone has cancer of the kidney that has spread elsewhere, and you take out their kidney, what might happen?Uchio It is not just taking it out, they have to get secondary therapy as well. If they're not a candidate for secondary therapy, we do not take the primary lesion out. We do what we call treatment with KIP, which is Kidney in Place. If you have significant metastatic disease, and the primary lesion is not that significant, the oncologist will treat initially with these new inhibitors or immunotherapy. If they respond, we can come back later, but if they are not going to get therapy, we do not take the kidney

out because taking out the kidney itself does not do anything; it is only with adjuvant therapy.Kluger Something unique about the kidney tumor itself, in addition to the immunotherapy that Edward just mentioned, is that kidney tumors are much more vascular, they contain many, many more blood vessels, so one possibility is that by removing the primary tumor, we are removing the source of all of the growth factors, all of the stimulants for the growth of blood vessels and other places in the body and that might itself help with the therapies that we are subsequently giving. It might also have an immune role as well if we do not remove the primary tumor, because that may be what is inhibiting the immune system to attack the tumors in the other sites in the body. We are not really sure what removing the kidney actually does, but it statistically it appears to help. Most of the new therapies that we have now, that Edward actually mentioned, we call TKIs, or tyrosine kinase inhibitors. It is a very technical term, but essentially these are very small little molecules that hit specific proteins in the tumor, or in the vessels, and stop the growth of the tumor. Some of them are in pill form, some of them are intravenous. Three have been FDA approved in the last couple of years and what we are seeing with kidney patients is that we can never really predict who is going to respond to which one. We are working on trying to do that, but at this point, we do not really know. I think just a few years down the road we are going to be facing a situation that is very similar to what we do in breast cancer. Using that as an example, breast cancer, once it metastasizes, there are many people who have a very good of quality of life for many years. We cannot cure them, but we treat it like a chronic disease17:36into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3 like with diabetes; we cannot cure them, but people take their insulin and they live their lives. The same with breast cancer where you give one therapy that may last for a few months or for a couple of years, and then it stops working so we move on to the next one. We have a whole menu of therapies that we can choose from and we are heading that way in kidney cancer as well. We think that we are going to soon have a whole menu of drugs. They are not going to help everybody, but they seem to be helping a fair percentage of patients and going forward, we are going to have additional things to choose from, and hopefully, options for patients who do not respond to either immunotherapies or therapies that work on the blood vessel system.Uchio This is a very exciting field and as Harriet knows, we study this in the laboratory and in our laboratory specifically, we study the von Hippel-Lindau gene. We are talking about a tumor that has a hereditary group where all of these patients form these tumors. When we look back at those tumors, we find a defect of this von Hippel-Lindau protein. If you look at people who just come off the street that do not have any genetic predisposition to this, the majority also have a defect in this von Hippel-Lindau protein. This von Hippel-Lindau protein is very active in this tumor angiogenesis, this blood vessel issue, and that is why these TK inhibitors that Harriet was talking about are so effective. They are effective with the tumor, but they do not cure, and that is why we concentrate on detecting it early, because with surgery we do cure. I mentioned adjuvant

treatment and I probably should not have discussed it in that fashion, because there really is no adjuvant treatment right now. We are doing clinical trials regarding adjuvant treatment after surgery with these high-risk tumors that are very large, anything greater than T1b, that have a high propensity to come back. In these clinical trials we are trying to give these medicines to see if we can decrease that recurrence rate.Miller There is the issue of angiogenesis, or the creation of new blood vessels, and it sounds like you have got some agents that work on that, but you just mentioned this gene for von Hippel-Lindau syndrome. Do you have something that sort of turns off that gene for that group of patients, or is that were the science is headed perhaps?Kluger Actually, in the patients that have the mutation, it is off.Uchio It is a tumor suppressor gene. But it has some downward pathways that actually turn on because of that, such as hypoxia-inducible factor 1 and 2, so there are a lot of targets for us, especially in our laboratory, looking at inhibiting these pathways for potential treatment modalities in the future.20:23into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3Miller Another question for both of you, is there a role for vaccines?Kluger Vaccines are being studied heavily for kidney cancer. Vaccines so far have not worked, but on the immunotherapy round that we were talking about earlier, interleukin-2 is a vaccine-like therapy in that it boosts the immune system, but it is not a vaccine in my mind. That is when you give dead cells or weaken cells into a patient and you activate the immune system. We are doing other kinds of immune stimulants. There is another drug called ipilumumab that we have given to melanoma patients fairly extensively and it is being studied as well for kidney cancer. The early studies are showing that there is activity. There are fair numbers of these immune stimulant drugs that are going to be coming down the pipeline and we will be trying them in kidney cancer as well.Miller In terms of your own research, what are some of the things you are working on that you are excited about?Uchio We are finding new pathways, not just the von Hippel-Lindau gene, the tumor suppressor gene being faulty, but what it effects in the pathways, what downstream pathways and potential targets, because you look at all these therapies and they do have side effects. We are trying to be very specific in our treatment, not like standard chemotherapy which does affect a lot of different cells that are rapidly dividing. We are actually hitting and inhibiting specific pathways. If you look at most of the research right now that is what we are looking at trying to find. We are also looking for new ways of diagnosing it by looking at tumor tissue arrays and genes and things that are up regulated in this cancer. Immunotherapy still is a hot field. If you look at interleukin-2, although the response rate is not as exciting as the new TK inhibitors you are talking about, these are durable responses. There are 10% that are actually cured and we do not get that with the TK inhibitors. I do not think that it is necessarily a treatment that has gone to the wayside, it has a lot of side effects and things but it is still an option. Kluger On the contrary, when we have a young, robust, healthy person who can handle interleukin-2 that is the treatment of choice. Only if it does not work on that patient do we go to the antiandrogenic approach, specifically for the reasons that Edward

just mentioned. We can actually cure the small percentage, or we can cure them with the interleukin-2, so we will try that first.Uchio That is why I send patients to Harriet at Yale Group, because not everyone is that aggressive, and what we are really shooting for is long-term care here.23:03into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3Miller What are some of the clinical trials that are available for people with kidney cancer, at Yale and elsewhere?Kluger We have a trial involving two drugs called, 5-Azacytidine and interferon. We are giving it for melanoma and kidney cancer and we have seen a couple of responses with that. We have a number of very novel therapies. They are all additional new, small, molecules that we are trying for patients to see if we can increase that repertoire of approaches.Miller Let me ask you sort of the same thing in terms of surgical approaches, are there any new technologies that you are working on that may make a difference for our patients?Uchio If you are talking about surgical and minimally invasive technology, there is new technology such as HIFU, which is a high-intensity focused ultrasound, where instead of putting the needle in, we can, like an ultrasound, put it on the side of the body and focus energy straight at the tumor. There would be no incisions, no piercing of the skin at all. That is not FDA approved in the US, but is in clinical trials, so there are things on the horizon and there are other things that I have been approached with by various biological companies trying to develop even more minimally invasive treatment. There is a lot out there, especially for the surgeon and even the interventionalist who is trying to treat these in a minimally invasive fashion. We have clinical trials looking at adjuvant treatments like we discussed and we work closely with the Natural Cancer Institute. They have a significant amount of trials looking at kidney cancer and also treatment for these hereditary von Hippel-Lindau proteins, and other hereditary cancers such as hereditary papillary renal cell carcinoma. We find that there are a significant amount of genes involved here and they form different types of kidney cancer.Miller This is not uncommon, but it also isn't an incredibly common type of cancer. When a patient is seen at the Yale Cancer Center, what type of multidisciplinary care do they receive and what goes into that?Kluger Usually the patient is seen first by the surgeon, though that is not always the case, sometimes they come to us first. We will then image the patient, using a CAT scan or an MRI depending on the patient and the specific situations, and we get pictures. Then we present the patient at our tumor board and at the tumor board we have a pathologist, a radiologist, surgeons and medical oncologists that will present. We discuss how to approach it. Sometimes it is better to give the systemic therapy, in other words the intravenous or pill, first and then try to take out the kidney. Sometimes we do it the other way around and that is the real advantage of having a multidisciplinary clinic.26:00 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-13-08.mp3Uchio The future is multidisciplinary and working together because we definitely want to start to get these trials going. Early on, if I see a metastatic patient, we will call the oncologist and make sure that they are aware and we definitely always have a tumor board and make presentations to make sure that we

get different opinions and get a collaborative approach to the treatment of these patients.Miller Unfortunately, it is still a very serious disease, and we do not have a cure for many patients, but is the prognosis improving overall for patients with this diagnosis?Kluger Overall it is, but we are also finding them smaller and we find less aggressive tumors, so we do not know if that is a real improvement in the prognosis. It sometimes takes time until you actually see the new drugs starting to help in prolonging life.Uchio We have been taking out the kidney or the tumor for a very long time so we know what cure rates are, especially when it is very small and still confined to the kidney. The real key now is to do it with less invasions to the body. We are trying to do this with a focused ultrasound and cryotherapy. Then, at some point, maybe the drug will be so good that we do not have to do any surgery at all.Miller It has been really interesting hearing about the advances, both in terms of surgery and in terms of medical therapy, and the collaboration between what the two of you do; it is great. I want to thank both Dr. Harriet Kluger and Dr. Edward Uchio for joining us on Yale Cancer Center Answers.Kluger Thank you very much.Uchio Thank you very much.Miller On behalf of the Yale Cancer Center, I want to wish everyone listening 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. Next week, we will look at the field of psychiatric oncology with Dr. Jimmie Holland. I am Bruce Barber and you are listening to the WNPR health forum from Connecticut Public Radio.