



Kidney Cancer - Hereditary Connections and Treatment

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Welcome to Yale Cancer Answers with doctors Howard Hochster, Anees Chagpar, and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it is a conversation about kidney cancer with Dr. Brian Shuch. Dr. Shuch is an Assistant Professor of Urology and Biomedical Imaging at Yale School of Medicine and Dr. Hochster is a Professor of Medicine and Medical Oncology.

Hochster So tell us a little about your background and your training.

Shuch Ok, well I am a urologist focused on urologic oncology and I spent 6 years at UCLA as a urology resident, which is one of the premier kidney cancer programs, followed by 3-year urologic-oncology fellowship at the National Cancer Institute in Bethesda, Maryland and I have been here at Yale now for 5 years focused on building a kidney cancer clinical and research practice.

Hochster I see and so you trained as a urologist and then specialized in cancer-related things?

Shuch Correct.

Hochster And amongst all the urologists, you have particularly focused just on the kidneys?

Shuch Correct, about 90% of my practice is dedicated to evaluating patients with kidney tumors.

Hochster I see. So how common are kidney tumors?

Shuch So the lifetime incidents of kidney cancers differs by, you know the patient characteristics, but in a man the lifetime risk is 2% and in a woman the lifetime risk is 1% and that equates to about 60,000 new cancer diagnoses a year in the United States.

Hochster And, you know there are lot of times that we find things on CAT scans, kind of things in the kidneys that may or may not be cancer I guess, so what should people know about that?

Shuch So the incidence of kidney cancer has risen about 4 fold since 1970 and that is largely due to what we call incidental or accidental detection. Many of these tumors were not destined to need treatment, they were probably going to be in the patient and found may be on autopsy or just never detected, so we have found that there is a higher instance of kidney cancer but largely due to what we call a incidental or basically detection by us imaging for other reasons, finding the tumors which were never destined to cause any trouble.

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- Hochster So what is the approach to dealing with these incidental kidney findings on a CAT scan that was done for another reason?
- Shuch So we know the mortality of kidney cancer has not changed. The number of patients dying each year has not changed and if we were to treat 4 times more kidney cancers than previously, you would expect that we start making a dent in the number of patients dying each year by treating ones destined to cause trouble. So we find the patient with a small kidney tumor, we are trying to assess whether this patient really needs to be treated. We know that we overtreat a large amount of patients and this term overtreatment is really treating a tumor which was not destined to cause any trouble during one's lifetime and this overtreatment and overdiagnosis is common in the field of prostate cancer where there is a big controversy of should we diagnose with PSA testing, and in kidney cancer we are about 10-20 years behind where we are in other fields and we have to try to convince older patients who have other comorbidities that the incidental tumor which is small is probably not causing them any trouble now and may not cause them any trouble in the future.
- Hochster Right. So lot of times we do not know what to do about small tumors if they are going to become bad or not, so what you do when you find something like this on a CAT scan for an asymptomatic patient?
- Shuch So we try to individualize treatment for each patient. Unfortunately, the current diagnostic ability of imaging or biopsy cannot completely rule out a patient having a benign or malignant tumor. So classically we have not done things like biopsy, but we are moving in that direction with new molecular testing, but we try to individualize care for an older patient with a small tumor, we try to offer them active surveillance, close monitoring, and then, if it changes, then offer intervention. We are still at an area, where if we have a younger individual, we do generally offer treatment as the patient may have many years of life ahead of them and we know when small tumors are left alone, they do have a slow rate of growth.
- Hochster So, you are going to watch a lot of people, you do not always have to go straight to surgery?
- Shuch Correct. The term we would like to use is active surveillance or active monitoring. So in an older patient who has competing risks of death, we consider active monitoring very safe, effective strategy where the patients are monitored with imaging every 4-6 months, and we can get basically a feel for the tumor's aggressiveness. If the tumor is barely changing, which happens with most tumors, we feel more confident that observation is going to be very safe. If the tumor is having a rapid change over short period of time, then we have to change our approach and do recommend active treatment rather than active monitoring.
- Hochster Ok, well that is very interesting. So who is that you are talking about familial kidney cancer? Can you tell us a little bit about what that is?

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- Shuch So we have about 18 known genes which when altered and in a patient's genetic makeup can predispose them to inheriting a higher risk of kidney cancer than the general population. These genes are able to be tested for similar to the more common genes which we are very familiar with like breast cancer gene, BRCA-1 or BRCA-2 or the colorectal cancer genes, what we call the Lynch syndrome family. There are similar genes like that in kidney cancer which can just greatly increase the risk of developing a tumor in the kidney and have other manifestations depending on the type of syndrome.
- Hochster So if my send off my tests, cheek swab to 23andMe, I am going to like be told I am supposed to get kidney cancer then?
- Shuch I am not sure of the current makeup of 23andMe, but the direct-to-consumer genetic testing is not things that we generally recommend because it is very difficult to counsel the patient appropriately. Someone may have a higher risk of developing a kidney cancer, but that needs to be discussed in the context of a meeting with a genetic counselor.
- Hochster So none of those genes mean you got a 100% chance?
- Shuch We are not really sure what they necessarily are testing for, so I can't really give you any strong recommendations.
- Hochster But I mean among the 18 that you are talking about?
- Shuch Yeah, among the genes which we test for in many of our panels, we have patients who need to be followed very closely for development of kidney tumors and other manifestations that may have specific management plans, how we would observe someone for their cancer risks.
- Hochster So who knows if they should get these, you know, see you and your clinic and get that kind of testing done.
- Shuch So we have recommendations for who with kidney cancers should get evaluated and those include someone with an early age of onset of a kidney tumor, we recommend age 45 or less based on my research while I was at the NIH, someone with bilateral kidney tumors, one in each kidney or what we call multi focality, multiple kidney tumors, or there are some associations with some skin manifestations or other types of cancers like melanoma or other ones depending on the syndrome. Now if you have a couple of first-degree relatives with kidney cancer, that also raises risk as well and if they had testing and they tested positive for a genetic change, you as a family member would want to be tested because you could be at risk of developing a higher predisposition.
- Hochster So if you are parent or a brother or sister who had kidney cancer especially early onset at a young age, then that is something people might want to look into.

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- Shuch So we would love to have the affected individual who has the cancer to be tested, because if they were to test negative for any of these strong genes, your risk if you are their child or a first-degree relative would be much lower, but we have patients who come in and they are anxious and we map out a family tree and we try to understand whether they should be tested as well.
- Hochster And you do this in your clinic.
- Shuch So we have a cancer genetics and prevention program at Smilow and I direct the GU cancer program where we see patients with hereditary or early onset cancers of the kidney, the prostate, or upper urinary tract as well, and they meet with me and a genetic counselor and we determine whether patient should be tested and if they do test positive, we try to come up with a comprehensive plan of action to get other specialists involved.
- Hochster I see, and the people who have these risks for kidney cancers, does that mean that they just would then land up having additional CAT scans, whatever testing?
- Shuch So for patients who have high risk, we have generally switched over to using MRIs which are very low risk of complications, the MRI has no radiation exposure, the contrast is very safe and we would periodically screen individuals with abdominal MRI scans for the kidneys and depending on the condition, it could be every year to maybe every 3 years. The conditions that have manifestations outside the kidney, we try to offer other types of surveillance, so someone who may have a risk of melanoma, we get them to see one of our melanoma dermatologists at Smilow or if someone had a high risk of, let's say, pancreatic cancer, we get them plugged in with screening what the clinician focused on that.
- Hochster Okay and so, you know there is still controversy about how useful mammography is for screening for breast cancer, so we do not have a lot of outcome data I take it on this approach?
- Shuch We don't have population based outcome data because these conditions are pretty rare or thought to be rare, but I would give, we have many anecdotal experiences of patients with a condition which is highly lethal when disseminated that if we detect early, we have cured by doing screening. So yes, there are no population-based recommendations that are based on randomizing patients to screening versus no screening, but in all the hereditary cancer groups that do this type of screening, we have plenty of patients who were likely cured with early intervention.
- Hochster And how do you track the cancer in these families; if you know somebody has one of the genetic abnormalities that predisposes to kidney cancer.

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Shuch So we try to have a comprehensive pedigree or family history and then if we find someone who is affected, we try to reach out to their other family members who may be at risk and it is called cascade testing, where you know who is at risk and then you could offer testing to those individuals and if they were to test positive for having the same inherited risk, not that they inherit cancer, they inherit a higher risk, then we try to get them plugged into a comprehensive screening program as well.

Hochster I mean do you remove kidneys preventatively?

Shuch So unlike breast cancer or with ovarian cancer risk, where someone who has had passed their childbearing age, may no longer need their ovaries, kidneys are vital organs, we cannot remove kidneys unnecessarily, loss of kidney function does predispose to things like chronic kidney disease. So we obviously would not want to do that, but we follow patients; if we find tumors early, they could be treated with things like partial nephrectomy, to preserve their kidney function and eliminate their risk of cancer dissemination.

Hochster And how do people who may be concerned about their familial risk of kidney cancer, how would they get an appointment, how would they reach you?

Shuch So we have a large clinic and we see patients twice a month with the genetic counselor and myself and it is a number, 203-200-4DNA which is the main Smilow Cancer Genetics program, and we basically before someone comes in, we give them a detailed family questionnaire to try to map out their family history, so when they meet with one of Smilow's cancer genetic counselors and me, we try to get a really good basically a picture of what their family is like.

Hochster So they can call 203-200-4DNA and say I am concerned about my family history of kidney cancer?

Shuch Correct.

Hochster Or for that matter for another cancer.

Shuch Correct.

Hochster And they will get arranged to see a genetic counselor.

Shuch Correct, we will have someone taking intake and then, they will give them the appropriate previsit questions so they can fill out and make the appointment even more valuable.

Hochster Well, thank you very much for that discussion on inherited kidney cancer. We are going to take a short break now for medical minute. Please stay tuned to learn more information about kidney cancer with Dr. Brian Shuch.

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Medical

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Hochster This is Dr. Howard Hochster and my guest, Dr. Brian Shuch and we are talking about kidney cancer. So Brian, we talked a little bit in the first part of the program about familial kidney cancer, that is pretty rare, you said incidents of kidney cancer in the United States lifetime risk is 2% and what percent of all cancer is kidney cancer?

Shuch Well kidney cancer is one of the top 10 malignancies, so probably 5% or less of the overall cancer is related to kidney and of those that are kidney, may be only 2-5% are hereditary.

Hochster So 2-5% of the 5%.

Shuch Correct.

Hochster It is still low number. So there is a lot of sporadic kidney cancer out there and we talked a little bit about active surveillance as a strategy when these are discovered, so what is the approach today for people who are diagnosed with kidney cancer, how do you treat these people?

Shuch So patients with early stage kidney cancer, what we may call may be stage I, localized kidney tumor, a lot of times, we try to discuss treatment based on the patient's risks and they say is all you have is a hammer, everything looks like a nail. So we do not try to do that one size fit all approach here, where if you see a tumor, you automatically cut it out. We have done active surveillance for that modality for older individuals. We also offer needle ablation for small kidney tumors that patients may not be good candidates for general anesthesia. We can stick a needle into the tumor and try to burn it or freeze it and this is also effective local treatment strategies and finally, we do a lot of partial nephrectomies where we would cut the tumor out and then spare the remaining kidney. We rarely take out a whole kidney nowadays for small tumors.

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- Hochster So that is good to know that even if you have kidney cancer, only part of your kidney will be removed.
- Shuch: Correct, we focus on oncologic cure and second, we focus on organ preservation and third, we try to avoid a large scar and in that priority.
- Hochster And so, is there particular size or is the CAT scan appearance or whatever that is going to help you decide on if people need surgery or not, again we are talking about a tumor that is just localized to the kidney.
- Shuch So when tumors are less than 2 cm, the new guidelines by the American Urologic Association does offer surveillance as a good strategy for initial management, but for tumors that are larger, we start to talk about active interventions and again, the ablation, the needle procedures where we do in conjunction with radiology, generally we do those for tumors 2-4 cm. When we get to a larger size tumor, 4 or greater, when tumors are localized, we still can talk about partial nephrectomy, but as the tumor gets to be very large, 7 cm or greater, we generally have to take the whole kidney out unfortunately.
- Hochster So 5 cm is like 2 inches, so if it is less than 2 inches, you know one and three quarters, then you are in that category where you are kind of may be watching, may be operating or ablating. You have a trial; I understand where you are prospectively collecting information on people who are not getting surgery.
- Shuch Yeah, we are trying to figure out which small tumors are ones that are destined to not change in size and which ones are destined to grow and need treatment, and understanding that would be very vital for patients who are newly diagnosed with a renal tumor where we would have a biomarker or a test which could tell the patient or reassure them, your tumor is not destined to grow and currently, we do not have that information available leading most patients who have anxiety to want to go under the knife and have treatment where many of them, the tumors may not actually be destined to cause any harm.
- Hochster So what is your trial doing?
- Shuch It is offering patients active surveillance or close monitoring. We do some novel imaging. We do some genetic evaluation of their tumor biopsy and then we closely characterize them with a very close follow up and if the tumor reaches the certain size threshold where we are uncomfortable or the patient is uncomfortable, then we have a quick trigger to offer treatment.
- Hochster Usually when you say uncomfortable, it is not like they are physically uncomfortable?

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Shuch It is they are just getting anxiety. These tumors rarely cause any symptoms and as just patient knowing that they have a tumor in their body and knowing that it is slightly growing, makes patients often have anxiety and want to elect treatment.

Hochster Right and why is that people usually do not have pain or discomfort from these kidney tumors?

Shuch Most of the small tumors, they are localized, the kidney is surrounded by a large area of fat, deep in the body, and there is not really any nerve fibers there to cause any discomfort. When you even see patients with very large kidney tumors, and we are talking of a size of a grapefruit, a lot of times patients still may not have any discomfort.

Hochster I see and how other than the fact that somebody may have gotten a CAT scan for another reason, how do these patients usually come to medical attention, what is that they notice?

Shuch For the classic triad prior to everyone getting scanned incidentally was the triad of having flank pain, having blood in the urine, and having the doctor feel or palpate a large abdominal mass.

Hochster That would be pretty big.

Shuch That would be very big. We see that less than 10% of the time nowadays.

Hochster But if there is blood in the urine, that's people will notice that usually.

Shuch Blood in the urine should not be ignored, it could be something very minor, but it could also be representative of a cancer which needs further urologic attention.

Hochster Okay, so that is I think we want to emphasize that is a sign, a medical finding that patients might notice and that really requires them to see a physician because there are lot of things that are benign or things that can be treated very early, but really it is not a good thing to ignore.

Shuch Correct.

Hochster Okay, so we counsel a lot about nonsurgical treatment options.

Shuch So when we have a patient who has advanced disease, we have multiple agents that are available systemically and there have been a plethora of systemic therapy options in our field when patients who may have their kidney removed or they present with metastatic disease. We have now 11 FDA-approved drugs for the treatment of advanced disease whereas prior to 2005, we only had 1.

Hochster That is a lot of progress in the last decade.

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- Shuch Definitely. It is one of the most exciting fields of cancer because we have made such progress in the past decade that we have so many agents and our patients are living longer than ever before.
- Hochster And so there is for people at high risk after surgery, there are some treatment that can help?
- Shuch So unfortunately we are left without a magic medication which will be given to reduce the risk of death. It is an area of our field where you take someone's kidney tumor out and you believe you have eradicated all the disease and that therapy would be called adjuvant therapy. We have no effective adjuvant therapies which change someone's overall survival. We have many trials in this area and most have failed. We have one drug which may slightly reduce time to recurrence, it is a pill called, Sutent, it is an oral pill, but the pill has side effects and even though the FDA did approve it last month, most clinicians feel that without changing someone's overall survival, we still have ineffective therapy to lower the risk of recurrence, but that does not mean we are not going stop trying and we have 2 trials open at Smilow Cancer Center, which are multidisciplinary trials working with our medical oncologist and our urologic oncologist, trying to employ some of these new novel agents, which we would call targeted immunotherapy to lower the risk of recurrence by harnessing one's immune system to attack maybe residual cancer cells and the goal being improving survival.
- Hochster So that is a very exciting field today, immunotherapy and harnessing the patient's immune system to kill the cancer. What is happening with that in kidney cancer?
- Shuch So kidney cancer is one of the rare cancers with melanoma that traditionally responded to immune therapy and the first FDA-approved drug for kidney cancer in 1991 was IL2, intraleukin2 and since that time, the field, since 2005 on focused on these targeted drugs, focusing on the tumor biology, but kidney cancer now has had a immunotherapy revolution where we are moving back to try to do first line immunotherapy for the treatment of metastatic kidney cancer with the drug Opdivo or Nivolumab that is now FDA approved for kidney cancer. We have now had positive data for other immune medications, one called Yervoy or ipilimumab which should be approved for the treatment of kidney cancer as there is positive trial when used in combination with Nivolumab that the treatment of upfront immunotherapy probably is the current standard of care for patients with advanced disease.
- Hochster So some of the treatments we have talked about are drugs like Sutent or sunitinib, that is a tyrosine kinase inhibitor, which kind of turns off the cell's growth signals and then now you are talking about immunotherapy that actually allow the patient's immune system to work better and so those are under active investigation at this time.

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- Shuch So both class of drugs are approved and we do have a lot novel trials open at Yale where we combine both classes of drugs together that my collaborators, Drs. Mario Sznol and Harriet Kluger are working on, but we try to combine both classes of agents and it seems that together they may be synergistic that they can have added effect to improve patient outcome, still under investigation, but we feel that our field will move forward with some of these novel combinations.
- Hochster That is very exciting. So you were saying that today before, people used to get interleukin-2 perhaps if they metastatic kidney cancer when that had come back and spread or possibly one of these drugs like Sutent, but now you are giving immunotherapy mainly.
- Shuch So our program is very focused on giving upfront immune medication and we feel that these immune drugs offer patients a greater chance for a more what we call durable response, meaning a response that will not just be shortlived, but one which will offer patients a long period of disease remission and our goal in our field is providing patients with the opportunity for a complete response that has been seen in the prior era with IL-2. With the new immune medications we have seen some patients having complete remission, we are hoping it for long periods of time, but only time will tell.
- Hochster So some of the trials going on now are kind of comparing things like standard immunotherapy, Nivolumab, to other combinations. Why should patients be interested in participating these clinical trials?
- Shuch So until we can prevent cancer from occurring and we can cure everyone, we know there is work to be done. So I would tell any patient who has cancer, a clinical trial is investigating new or novel therapies which are believed or hope based on a lot of data from the laboratory to be better than what is the existing standard of care. So many of the trials we have here are combining agents which can be given by any doctor with an additional medication which has strong rationale to be used in combination, and we are hoping to improve the outcome, and we are not going to rest until all our patients can be treated effectively with medication which will eradicate the disease and we are far from that and we hope that in the future we'll have the ability to provide those types of outcomes to greater patients.

Dr. Brian Shuch is an Assistant Professor of Urology and of Biomedical Imaging at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer right here on WNPR.