

Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



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Advances in the Treatment of Kidney Cancer

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week, Dr. Foss is joined by Dr. Brian Shuch for a conversation about kidney cancer. Dr. Shuch is Assistant Professor of Urology at Yale School of Medicine. Here is Francine Foss.

Foss Let's start off by having you give our audience a very brief update on your training and how you actually came here to Smilow.

Shuch I am from New York originally and grew up about an hour away from Yale. Both my parents were involved in education and it got me interested in research and teaching, but then I ended up following my sister to college at the University of Michigan and returned back East for medical school at NYU where I became interested in oncology and urology. At that point, I knew I wanted to do urology and I was fortunate enough to end up matching at a program at UCLA, which was very strong in urologic oncology and kidney cancer. After that time, after my six years in Los Angeles, I wanted to pursue additional urologic oncology training and I spent the past three years at the National Cancer Institute in Bethesda, Maryland. I have been at Yale about two months after being recruited here by a dynamic and exciting chairman, Dr. Peter Schulam who is inaugural chair of the Department of Urology. I met Dr. Schulam while he was at UCLA and he had trained me to do minimally invasive surgery. I had many offers, but I saw the exciting things that Dr. Schulam was initiating at Yale and I recognized an opportunity to build a really strong kidney cancer program here, so I am thrilled to be in New Haven.

Foss And we are thrilled to have you here.

Shuch Thank you.

Foss Can you talk to the audience a little bit about the whole area of kidney cancer? We do not talk about it very often on the show. Can you tell us how common kidney cancer is and how it presents clinically?

Shuch Kidney cancer is fairly common, and in terms of how it presents, the presentation of kidney cancer has drastically changed over time. In the past, the patient would present with a classic triad, where they would have flank pain and they would have blood in the urine, and they would have an abdominal mass. Now these things are very, very different. Most patients present incidentally when they come to the ER or have a test done by their primary care doctor. This has actually changed the overall incidence of kidney cancer. Instead of being about 30,000 cases a year, now it is about 60,000 cases a year. It accounts for about 3% of all cancer deaths in the United States. Among men and women it is the 6th and 8th most common cancer and today, in someone's lifetime, they have a 1%-2% chance of being diagnosed with kidney cancer.

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- Foss And again a lot of that is due to the fact that these are found incidentally now?
- Shuch Correct, people go to the ER, they have abdominal pain or they might have some back pain and then they get imaged and they are found with a small tumor. The greatest increase in the incidence of kidney cancer now is actually found in tumors that are small, between 2 cm and 4 cm. It is actually debated whether treatment for those is required.
- Foss Can you tell us why kidney cancer falls under urologic cancers? We typically think about the bladder and the ureters, how does kidney cancer fit into that whole picture?
- Shuch Urologic oncologists are trained during their residency and fellowship to manage all forms of cancer within the urinary tract. So as part of our training we managed tumors of the adrenal gland, just on top of the kidney, the ureter, the bladder, the prostate, the testicles, and the penis. These cancers make up approximately 25% of the total number of cancers in the United States. Prostate cancer is the most common cancer we see. Kidney cancer is actually third right behind bladder cancer with about 60,000 cases a year in the United States.
- Foss When you think about bladder cancer you think about risk factors associated with that and smoking being one of them. Can you talk about risk factors for kidney cancer?
- Shuch With kidney cancer there are well-defined risk factors. We do know from one of my former mentors at the NCI who has now moved to MD Anderson, Dr. Wong-Ho Chow, that there is great epidemiologic evidence that hypertension and obesity are very much linked to the development of kidney cancer. There are some other risk factors that may be associated with it, there is a small increased incidence with smoking, African Americans have increased incidence as well and there are some hereditary factors that have long been known to influence the development of kidney cancer.
- Foss And can you contrast that with the risk factors for bladder cancer?
- Shuch For bladder cancer, the number one risk factor is smoking, and now when we see a patient with bladder cancer and they are a current smoker we definitely try to get them to quit smoking because it actually decreases the risk of recurrence and could be lifesaving.
- Foss Can you talk a little bit about the age distribution, you mentioned African Americans have a higher incidence, but can you talk about age distribution for kidney cancer? When do you start seeing it and how old are people on the older end?

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- Shuch The median age of kidney cancer is 64 years of age. And the incidences widely vary. There is actually a project that we studied at the NCI looking at what defines someone to have early onset kidney cancer. The majority of kidney cancer cases are between age 50 to age 75. There are some outliers, it is very rare to see someone who has kidney cancer at age 20 or 30. Something strange is going on with that person. You have to wonder why they developed kidney cancer, less than age 46 is actually lower than the 10th percentile of kidney cancer.
- Foss Are there other kinds of tumors that involve the kidney? If you have a mass on your kidney, what is the chance that is kidney cancer versus another kind of cancer that is presenting in the kidney?
- Shuch Kidney cancer is a general term for cancer that arises from the kidney. The most common type of cancer of the kidney is what we called renal cell carcinoma, and that is actually cancer arising from the functional unit of the kidney, which we refer to as the nephron. That nephron is responsible for the formation of urine. There is another type of cancer of the kidney which occurs in about 5% of patients and is actually similar to bladder cancer and that is called renal pelvic cancer and it is from the lining and it is very similar to the risk factors for bladder cancer and under the microscope it looks very similar. There are a group of benign tumors which arise from the kidney and those ones do not have the ability to spread and some of those we see and treat as well.
- Foss So other than finding a lump on a scan incidentally in the ER for instance, what is the other way that a patient with kidney cancer can present?
- Shuch Prior to this explosion in cross sectional imaging, CT and MRI, the historical presentation was that triad which was flank pain, abdominal mass and blood in the urine, that was a classic presentation, however, kidney cancer was also called the internist tumor because it can mimic many benign and cancerous conditions due to non-specific findings, the tumor would secrete things which would cause increase in calcium, weight loss, fevers, or low blood count. Today, with widespread imaging, it is very rare, but if you do have some symptoms such as abdominal pain, flank mass, blood in the urine, you should clearly get medical attention, however, today that presentation is rare. It occurs in less than 10% of the patients we see now-a-days.
- Foss Brian can you step us through the process of diagnosing a kidney cancer and then getting a patient to treatment?
- Shuch When you see a kidney tumor on cross sectional imaging, the first thing you want to know is if that tumor is enhanced when you give someone IV contrast, does it actually become brighter? Tumors that enhance in the kidney are almost always a type of growth or neoplasm in the kidney, it could be benign, it could be malignant. In someone who has no evidence of metastatic disease it is usually arising from the kidney. There has been discussion of the role of biopsy. Renal biopsies have traditionally not been performed for kidney tumors because it is very difficult to distinguish the benign tumor from the malignant tumor, and classically they have recommended excision even

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without a biopsy. At Yale we are exploring the role of biopsy and using molecular markers to potentially select patients who would have benign tumors and spare them potential unnecessary procedures.

Foss So the procedure for most patients would be to go to the operating room and have that kidney removed completely, or just the mass removed?

Shuch In terms of someone with a large kidney tumor that is localized, the standard of care classically has been removal of the whole kidney, a radical nephrectomy that has been described in literature for the past 50 years. However, it has emerged that removing only the tumor, which is called a partial nephrectomy, has become a feasible option. Initially that type of treatment was reserved for the patients with bilateral kidney tumors if they were at risk of going on dialysis, obviously you do not want to render a patient dialysis dependent, however, partial nephrectomy has expanded because there have been some real interesting studies showing that a partial nephrectomy potentially could spare someone the risk of chronic kidney disease that you would have with a radical nephrectomy.

Foss So when you do a partial nephrectomy the part of kidney that stays is basically functioning normally?

Shuch Correct, you do have some diminishment of renal function, especially if you have clamped the kidney for a long period of time or you take a very large piece of the kidney out if it is a very large tumor, but you can expect to spare a significant portion of that kidney.

Foss How often when you do surgery, do you find metastatic disease outside the kidney?

Shuch Now-a-days with CT and MRI imaging and complete staging, it is not very common to go into surgery not having detected metastatic disease. Kidney cancer is one of the unique diseases where even if you have metastatic disease, there is a role of a debulking nephrectomy. If you have a large bulky tumor and you have a small amount of the disease outside the kidney there is a clear survival benefit of doing surgery, however, sometimes intraoperatively we do find enlargement of lymph nodes and we do remove those to the best of our ability.

Foss Can you tell us other sites that it can metastasize to?

Shuch The most common sites of metastases besides the regional lymph nodes are the lungs, bone, the liver, the brain, they are all very common sites.

Foss Is there a role for radiotherapy either before or after surgery?

Shuch There is no real role. This tumor has classically been considered radio resistant. There have been some studies looking at radiating metastases to the brain and in patients who have brain metastases

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they may be able to avoid surgery with a new technology called radiosurgery, which we have at Yale. And that potentially can treat patients in a palliative way but for a primary tumor it is definitely not the standard of care.

Foss Patients oftentimes ask us questions such as, how long have I had this tumor? Is it slow growing? Has it been there for years? What do you generally tell them about kidney cancer?

Shuch There is no real way to know. You cannot look at a crystal ball and know how long something has been growing for, but we do know from patients with small kidney tumors that when they have been followed, the rate of growth is actually quite small. Some of those tumors grow about 2 mm a year. We do say for patients who have a hereditary cancer syndrome, known as von Hippel-Lindau it may take 10 years to 15 years for tumor to reach 3 cm. So a lot of times these things are not rapidly exploding, but occasionally they can.

Foss We are going have to take a short break for a medical minute. Please stay tuned to learn more information about kidney cancer from Dr. Brian Shuch.

*Medical
Minute*

Breast cancer is the most common cancer in women. In Connecticut alone approximately 3,000 women will be diagnosed with breast cancer this year but there is new hope. Earlier detection, noninvasive treatments, and novel therapies provide more options for patients to fight breast cancer. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection, and a healthy lifestyle, breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to make innovative new treatments available to patients. A potential breakthrough and treating chemotherapy resistant breast cancer is now being studied at Yale combining BSI-101, a PARP inhibitor with the chemotherapy drug irinotecan. This has been a medical minute brought to as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined today by my guest Dr. Brian Shuch. Brian is here to talk with us about kidney cancer and we have had a lot of discussion about how kidney cancer presents and the surgical procedures to remove the tumors. But I wonder Brian, if you could take a step back and talk with us a little bit about screening methods that are available for kidney cancer?

Shuch Unfortunately there are no real methods for screening for kidney cancer. There is no approved tumor or urine marker; however, it is something our team is very interested in pursuing. Imaging all patients as part of the screening program is not believed to improve outcome. This has actually been looked at in Asia and Europe, and randomly screening all patients pretty much finds a renal tumor in about one in every thousand individuals. In the US, it has not been considered worth the

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risk to screen patients due to radiation exposure, due to CT scans, the need for contrast imaging from MRI or CT and the anticipated cost. However, some argue that ultrasound could be a safe alternative for screening but it is not the most sensitive modality to detect small tumors. In specific populations, it may be beneficial to screen and those populations include those with a strong family history of kidney cancer.

Foss If a patient does have one of these small tumors, then you are not going have it excised right away, they are on active surveillance. Can you talk a little bit about what that is, how long does that go on for? Which is the best test and what are the outcomes from that kind of approach?

Shuch It is very interesting, despite the explosion in the number of kidney cancer cases a year the mortality has remained quite stable. So this has led many investigators to believe we are over treating these small renal tumors that were not destined to create any harm. So active surveillance is a way where we basically closely monitor a small tumor and we assess at interval periods of time the growth of the tumor. In prostate cancer this has been considered more of a standard of care and is actually endorsed by the MCCN and the American Cancer Society. In kidney cancer we are probably several years behind that. When I see patients who have a small renal mass I obviously want to see if they have any comorbidities, if they are healthy. A lot of people have reserved active surveillance for those sick individuals, however, I believe that we need to do more active surveillance and I do so by talking to the patient, going through the data on active surveillance knowing that these small tumors grow very small and the risk of having them spread is actually extremely low, one if they do not enlarge during follow-up, and two, if they do not reach a certain size threshold, which is about 3 cm.

Foss Are there any molecular tests that we can do on these tumors now to predict which ones are going to behave badly? We are hearing a lot about using genomic profiling to identify good and bad prognosis genes and I am just wondering if there is any way that we can do this yet with kidney cancer?

Shuch There is no real way to do it. We are actually about to open a clinical protocol where we will find the patients who would like to pursue active surveillance and we would do a biopsy at the start of the protocol and we would do sequencing, look at gene expression and also look at imaging characteristics and then we would follow patients, and if patients get nervous, or if they reach a predefined threshold where they should have surgery, we would intervene and then after the protocol we would look to see if there were biomarkers which would be able to predict patients having no growth and those biomarkers could potentially be studied in the future to say, you have a small tumor but we can spare you the risk of the procedure because you have a low risk of progression.

Foss At this point, this is a clinical trial?

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Shuch Correct, and active surveillance is considered a standard approach by the American Urologic Association.

Foss So if a patient is interested in this clinical trial, how would they go about entering the trial?

Shuch We are going to have the trial posted on the clinicaltrials.gov web page once it becomes available and it will be on the Yale Urology website.

Foss For the general patient, what are the treatment options for patients that have been diagnosed with renal cell cancer?

Shuch For patients who have localized kidney cancer, the standard of care has been surgery, whether it be partial or radical nephrectomy, for small tumors active surveillance is again an approach. There is an emerging type of procedure where you actually stick a needle and either burn or freeze a tumor, which is called ablation. We have reserved that for patients who are elderly or where surgical section would not be considered safe for those patients.

Foss When the patient develops metastatic disease, I presume that you work with your colleagues in medical oncology to administer chemotherapy?

Shuch I chose urology to be involved in systematic therapy and I have given systematic therapy for about five years and while at the NCI I had experience running clinical trials with some novel agents. I am working with two of our medical oncologists here Dr. Mario Sznol and Dr. Harriet Kluger but I also give systematic therapy as well for kidney cancer. Most of these are oral targeted agents which are approved by the FDA.

Foss Can you tell us a little bit about those treatments?

Shuch These treatments have been approved, and basically by understanding the molecular biology of clear cell kidney cancer we understand there is up regulation in a lot of pathways. Basically these drugs act to put the brakes on these pathways. Most of these drugs are oral and they are targeted, they decrease the progression. They seem to improve overall survival, however, these drugs are not curative and even though there have been seven new drugs approved in the past seven years, there is a lot of work to be done and that is why clinical trials are important to come up with a future therapy that could potentially cure patients of metastatic disease.

Foss What about the role of the immune system and some of these new immunomodulatory therapies? Are they effective in kidney cancer?

Shuch Classically, melanoma and kidney cancer have been two of the most immunogenic cancers. IL-2 was the first FDA approved drug and interleukin-2 actually can cause a complete response in about 7% of patients. There are two classes of drugs that are in trials now, one is the CTLA-4 antibody

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that has shown to be beneficial in melanoma and is approved. For kidney cancer, and monotherapy, it is not the best agent, there are some side effects. A class of drugs, which basically has been developed due to some of the work by a Yale investigator, Dr. Lieping Chen, are drugs called PD-1 and PD-L1 inhibitors and those cause the immune system to wake up to go ahead and attack the kidney cancer. Those are being tested in a lot of solid tumors, and for kidney cancer it appears very promising, but it is still early and phase 3 trials comparing that therapy are just getting underway.

Foss It used to be 10 or 15 years ago that we had no way to treat kidney cancer, so this is really very exciting that we have these new treatment approaches.

Shuch It is actually very hard to keep up, and urologic oncologists and medical oncologists are faced with eight agents that they have and we do not know what the optimal schedule is, when to give what drug, when to give the other drug. It is great for patients that they have a lot of options, but we still have a lot of learning to do to see what are the optimal combinations or what the optimal schedule is.

Foss Can you tell patients today that we have made an impact in this disease? Can you tell patients that they are probably going to live longer because of these new treatments?

Shuch In this era, we do know if patients are living longer due to better supportive care, or due to the agents that we have available, it is hard to say for sure which is the driving force behind that, but we know that patients are all living longer and we do feel like these agents are able to be given and tolerated in a greater number of patients than in prior treatment eras.

Foss Can you talk a little bit about the inherited renal cell cancer? We mentioned that some of these patient's have hereditary renal cell cancer, can you tell us how that is different than the de novo renal cancer and is there a different treatment?

Shuch Many years ago it was recognized that kidney cancer could run in families. Prior to 1990, there was only one described hereditary cancer syndrome and at that time it was believed that only 1% to 2% of kidney cancer was hereditary. In studies from epidemiologic data bases from Iceland and Sweden we actually know that kidney cancer has a very strong hereditary component and in fact, 80% of kidney cancer that we see occurs in about one-fifth of the population. Today, with the amazing explosion of genomics, we understand there are about 14 different hereditary cancer syndromes that are associated with kidney cancer. So about 5% to 10% of kidney cancer that we see is considered hereditary, that may be associated with a predisposing genetic change.

Foss Do all patients with kidney cancer get these genetic studies done to see if they have those genes?

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- Shuch We are developing a program at Yale where we are specifically targeting the patients who would have high risk for a hereditary or genetic cause. Any individual less than 45 is going to be recommended to undergo genetic testing and that was some of my work at the NCI, and that paper is coming out in the Journal of Clinical Oncology. The patients younger than that age have such a high risk that it justifies seeing a genetic counselor. So teaming up with Ellen Matloff, Allen Bale and their great genetic counseling team, we are formulating a program where the patients who would have bilateral or multifocal tumors or other associated cancer types, would come and get screened.
- Foss What is the screening program for these patients?
- Shuch They would come and see a urologist, they would also come to see a dermatologist and also Ellen Matloff and Allen Bale and the genetic counseling team. You might say, why a dermatologist? And some listeners might be confused by that, but half of the syndromes we see actually have a dermatologic manifestation. Some are just benign skin bumps, some may be conditions such as melanoma, and is actually not uncommon to see patients who are referred by an astute dermatologist that recognizes these lesions and then refers the patient to a urologist for a suspected kidney cancer syndrome and is not unheard of that they would be found with a large tumor and have surgery prior to that tumor spreading.
- Foss Can you clarify for the audience what kind of family history they should be looking for that would put them at risk for kidney cancer? Is it just family members with kidney cancer or are there other things?
- Shuch If you have one or two first degree relatives or second degree relatives with kidney cancer, it is obviously a sign that there could be something genetic, but there are now 13 or 14 different cancer syndromes that are associated with kidney cancer. Some are associated with melanoma and kidney cancer and others are associated with what we would call adrenaline producing tumors, or pheochromocytomas or paragangliomas. There is a class where the patient gets pancreatic tumors and kidney cancer. There are also ones that get uterine fibroids. We have women who have hysterectomies at age 20 or 30 and they have a condition which is associated with early onset fibroids, kidney cancer and skin lesions. There is another one associated with GI stromal tumors. It is very complicated and a lot of urologists are not very familiar with these syndromes since they have been recently described, and that is why we hope that our new program will be available to patients throughout the State of Connecticut and the surrounding regions. We are all familiar with these syndromes and we can tell them if they have a generic predisposition for getting kidney cancer, and have them screened, as well as their family members, if they are found to have a genetic cause of kidney cancer.
- Foss So anybody in Connecticut or this regional area could come to your clinic to get screened?

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Shuch Correct, we have an amazing genetic panel where we basically can screen the patient for multiple hereditary cancers being associated with kidney cancer, and it is a multidisciplinary network of providers who work together to identify a genetic cause. We have excellent pathologists, molecular pathologists, and we are able to also identify some of the changes that may signify a hereditary syndrome.

Foss In this day of insurance concerns, is this paid for by most people's insurance?

Shuch Insurance does pay for genetic testing. There is a whole complex related field regarding genetic testing, and Ellen Matloff's team is quite experienced in discussing the implications of genetic testing. Before you actually do genetic testing, you need to sign the consent, you need to have counseling to understand what the implications are because obviously if you are found to have a hereditary cancer syndrome it opens up a whole can of worms, do you tell other family members, do you have your kids screened, so it is quite complicated, but the Yale Genetic Counseling Program is well experienced and they are used to dealing with this. They have been focused on colorectal and breast, and now they are planning to include a kidney cancer program.

Foss Just in the last minute, are there any other clinical trials that you want to tell us about?

Shuch The one that I mentioned about active surveillance, biopsying and looking at molecular markers is something we would like to have available soon. The other one that we are submitting to a biotech company is working to get a drug where we would give patients with a large localized tumor that would go for radical nephrectomy, a drug to shrink the tumor and if we are able to shrink the tumor to a significant size, we would potentially be able to do a partial nephrectomy or an ablation on the kidney tumor and spare them the risk of having renal insufficiency. So the goal is to downsize the tumor in term of a neoadjuvant approach which is common in other types of cancers, but has not been common in kidney cancer because prior to this treatment era, immunotherapy was the only approved drug and it does not affect tumors. However, we do know from the patients who did not go for nephrectomy that these drugs do cause some downsizing. We hope to use that to change the treatment paradigm.

Dr. Brian Shuch is Assistant Professor of Urology at the Yale School of Medicine. If you have questions or comments, we invite you to visit yalecancercenter.org where you can also get the podcast and find written transcripts of previously broadcast episodes. You are listening to the WNPR Connecticut Public Media Source for news and ideas.