

Yale CANCER
CENTER
answers

WNPR Connecticut Public Radio



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Understanding Kidney Cancer

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. 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 1888-234-4YCC. This evening Ed welcomes Dr. Harriet Kluger. Dr. Kluger is an Associate Professor of Medical Oncology at Yale School of Medicine and she is an expert in the treatment of kidney cancer.

Chu Why don't we start off with a brief overview of kidney cancer? Can you tell us how significant kidney cancer is in terms of a public health problem?

Kluger It's one of the most common kinds of cancer. There are 57,000 new diagnoses in the United States each year. There are around 11-1/2 thousand deaths each year. The incidence of kidney cancer has actually gone up, but it might just be because we are getting better with diagnosing them and picking them up earlier, and these cases actually were there and went along undetected over many years before we started using CAT scans frequently.

Chu It's interesting, I have to say I don't think of kidney cancer as a common disease, but when you say that there are 57,000 cases, that's pretty significant.

Kluger That's right. Just to give you a reference point, the incidence of breast cancer is 220,000; it's about a quarter of the incidence of the more common diseases.

Chu And in what age group does kidney cancer typically develop?

Kluger It peaks in the sixth and seventh decades, in other words people in their 60s and 70s, sometimes we see younger and we see older, that's just the average incidence.

Chu And what do we know in terms of the risk factors for kidney cancer?

Kluger A number of risk factors have been established. Smoking, obesity, high blood pressure, acquired cystic disease, and a number of other chronic kidney ailments predispose people to getting kidney cancer. Certainly patients who are immunosuppressed are more likely to get it, such as kidney transplant patients or other organ transplant recipients who are on chronic immunosuppression.

Chu What do we know about the genetics, is there a familial predisposition? If say a family member has developed kidney cancer?

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- Kluger Yes, there can be. Most of the cases are what we call sporadic, in other words isolated incidences, but there are a number of genetic syndromes that have been identified over the past years. The most common one is called von Hippel-Lindau syndrome, which is basically a problem with the formation of blood vessels, and in those patients we see a higher incidence of kidney cancer. There are a number of other hereditary syndromes that have been identified as well.
- Chu Say for instance, in this von Hippel-Lindau syndrome, will the kidney cancer develop at an earlier age or also develop in the 60s and 70s?
- Kluger It tends to develop earlier on and they tend to have multiple kidney cancers.
- Chu And is kidney cancer just one disease, or are there different subtypes within that big diagnosis?
- Kluger There are a number of different subtypes. The most common type is called renal cell carcinoma. That type arises from the cells of the kidney that are responsible for draining out fluids, getting rid of toxins that we drink, getting rid of extra salts and so on, but there are other cells within the kidney and cancer can certainly arise in those cells as well. We can have transitional cell carcinoma of the kidney, which is more like a bladder cancer that arises from a different part of the kidney. You can have tumors of the blood vessels within the kidneys and so on. But those are rare. The renal cell carcinomas comprise about 90% of all of the kidney cancers and the other group is around 10%.
- Chu Do kidney cancers typically reside within the kidneys, or can they spread to other parts of the body?
- Kluger They can spread to other parts of the body as well and that of course relates to the likelihood of survival. We use what we call a staging system, and it's used in many cancers. You can have stage I to stage IV kidney cancer. In general, stage I would be a small cancer up to 7 cm in size that's confined to the kidney. Stage II would be over 7 cm, but still confined to the kidney. Stage III would be a kidney cancer that's invading adjacent structures, like the adrenal gland, which sits just above the kidney. It can invade into the tissues around the kidney or into a single lymph node and that of course is associated with a slightly worse prognosis. Then stage IV kidney cancer is cancer that's either spread to more lymph nodes or spread beyond the tissues that surround the kidney, or even to distant organs such as the bones and the lungs and so on.
- Chu For a lot of different cancers such as colon cancer, breast cancer, cervical cancer, and

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prostate cancer, we have screening and early detection methods that have been developed. Is there any such screening or early detection methodology that's been developed for kidney cancer?

Kluger It's not being used because it's probably not as common as the diseases that you just mentioned. In patients that have a very strong family history of kidney cancer, you can look at urine cytology and see if cancer cells spilled into the urine, or you can use screening ultrasounds and sometimes cases are picked up in that fashion, but it's only done when there is a very strong family history of it or when the patient has a unknown genetic abnormality such as the von Hippel-Lindau syndrome that we talked about earlier; at this point there is no standard screening method.

Chu For an average risk individual, which would be the vast majority of people who are listening this evening, there really is nothing that we can recommend as of 2009?

Kluger That's correct. Even patients who have the risk factors that I mentioned like hypertension, obesity, and so on, there is nothing that is done at this point.

Chu What are the symptoms that are typically associated with an underlying kidney cancer?

Kluger There is what we call the classic triad of symptoms, its pain in the flank, blood in the urine, and a palpable mass. Now in the old days, most patients actually presented with at least two of the three classic symptoms. Nowadays, with increased use of all sorts of imaging for other purposes, more and more patients are having their diagnosis made incidentally; people get a CAT scan for something else and/or an ultrasound for something else and the kidney cancer was seen.

Chu So is palpable mass a mass that the individual him or herself can feel, or a mass that only the physician could probably feel?

Kluger If they are really big, the patient can feel them, because the kidney is sort of at the back of the abdomen, it has to be really big for a patient to notice in nascence.

Chu So the main symptoms that might cause someone to go seek further attention would be pain, difficulty urinating, blood in the urine, and flank discomfort?

Kluger Correct.

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Chu And if those symptoms should occur, what should individuals do? Who should they see first in terms of medical attention?

Kluger Typically people will go to see their primary care physician first, and the primary care physician would probably order an ultrasound to work up the pain.

Chu And if an ultrasound comes back and it shows a suspicious mass in one of the kidneys, what would be done next?

Kluger It's interesting, in most other diseases if there is a mass or a tumor somewhere in an organ we go ahead and biopsy it. With kidney cancer, for the most part, we don't do that and that might be because of an old dogma, there were incidences in the past where patients had a biopsy and there was tracking of tumor cells along the biopsy area, and that's why its not done in kidney cancer, but in fact, its probably a rare side effect of biopsies but the standard of care has not changed. The radiologists are pretty good at defining cancer versus non-cancer based on the appearance of an x-ray or CAT scan more so then with many other diseases, and so if it's suspicious it gets taken out rather than biopsied for the most part.

Chu Taken out by a surgeon, or who would be the one to take out that kidney tumor?

Kluger The patient will then be referred to a urologist. There are a number of urologists at Yale who specialize in kidney cancer. The tumor can be removed laparoscopically if it's not too big, and that is a real breakthrough in the surgical approach because patients recover from the laparoscopic surgeries so much quicker then they do from open surgeries even if the cut is relatively big, because if you are taking out an 8 or 10 cm mass it has to come through somewhere so the cut in the skin may be big, but the recovery is still very-very quick. Patients are up within days and walking around and feeling much better very quickly. So, laparoscopic surgery when feasible, when the mass isn't too big and not invading adjacent structures, that's probably a good way to go, otherwise open surgery for removal is another way. If a patient has kidney disease, for example, if they have got some cystic kidney disease and the rest of the kidney isn't functioning all that well, and if it's a small tumor, you may not want to remove the whole kidney, so we can do what we call a partial nephrectomy, removal of part of the kidney, and that's typically done with open surgery. There are other methods if the patient is very old and not a candidate for surgery, you can have radiofrequency ablation or cryoablation, where you freeze the tumors, and those appear to be fairly effective in certain individuals.

Chu I would think that in determining whether or not a patient could undergo surgical resection of

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that tumor, one would want to make sure that the kidney cancer hasn't spread beyond the local confines of the kidney?

Kluger Yes, patients typically have a CAT scan of the abdomen and pelvis and a chest x-ray. We will sometimes order a chest CAT scan as well. On occasion, even if the cancer has spread beyond the confines of the kidney, we still remove the kidney and again that's a little different than the paradigm that we use to treat most cancers. There are a few patients who have what we call spontaneous regression of metastases, meaning if a patient has cancer that spread to the lungs as well and you remove the kidney tumors, there are a certain percentage of patients whose lung tumors will actually shrink when you remove the original tumor from the kidney. We used to think that that's because of immune reactions, you are activating the immune system or you are removing something that suppresses the immune system in the kidney, but there is another possibility; the tumors in the kidney create a lot of hormones that make blood vessels in tumors and when you remove the source of those hormones, you might actually be removing what makes the blood tumors grow in the tumors in the lung and what makes those tumors thrive. If we have a patient who can handle the surgery and in whom the bulk of the disease is in the kidney, even if it is spread beyond the area of the kidney, we will still remove the kidney and that has been shown to be associated with improved survival as well, as opposed to leaving it in.

Chu Terrific, and once surgery has been done is there any role for any additional therapy?

Kluger If the patient has metastatic disease, disease that spread, then yes, we definitely try to treat those tumors and we can talk about that a little more because we have a lot of options there. If there are no visible tumors left after we have removed the kidney, then the question is should we give what we call adjuvant therapy, adjuvant meaning boosting. And why would you do that? Because there is a possibility that very-very small foci of tumors have already escaped from the area of the kidney and overtime they can grow. Adjuvant therapy is given in other diseases like breast cancer and colon cancer after you have removed the tumor you go ahead and given some additional chemotherapy. Currently we have a very big clinical trial looking at the role of adjuvant therapy in kidney cancer. There are two drugs that have been showing to be effective in metastatic kidney cancers. Patients can either one of the two drugs or observation, and hopefully we will have the answer to that over the next four or five years.

Chu Harriet, can you tell us what those two drugs that are being tested in the adjuvant center are?

Kluger They have got lovely names. One is called sorafenib and the other one is called sunitinib.

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They are actually fairly similar, they target the whole blood vessel factory within the kidney tumors and again the thought is that if you give it for a year after resection of a primary tumor, maybe we will be starving tiny metastatic foci of their blood supply and not enabling them to grow.

Chu Is there any role for radiation therapy to be given after a surgery has been performed?

Kluger Not in this disease. The kidney cancer cells themselves are very resistant to radiation therapy and we tend not to use it. We certainly don't use it as adjuvant therapy, so in other words to sterilize the area after a cancer has been removed. We do use it down the road if a patient develops metastatic disease and we need to do it to control pain in the bones and so on; particularly if these are areas that can tolerate high levels of radiation that are required to kill the kidney cancer cells.

Chu You are listening to Yale Cancer Center Answers and we are here this evening discussing kidney cancer, detection, and treatment with Dr. Harriet Kluger from Yale Cancer Center.

*Medical
Minute*

There are over 10 million cancer survivors in the US and the numbers keep growing. Completing cancer treatment is very exciting, but cancer and its treatment can be a life changing experience. After treatment, the return to normal activities and relationships can be difficult and cancer survivors may face other long-term side effects including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated Comprehensive Cancer Centers such as Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

Chu Welcome back to Yale Cancer Center Answers. This is Ed Chu and I am here in the studio this evening with my guest expert Dr. Harriet Kluger, Associate Professor of Medicine and Medical Oncology at Yale Cancer Center. Before the break we were talking about the surgical approach to kidney cancer, can we take a step back and talk about the multidisciplinary approach to treating patients with kidney cancer? What is the approach that you and your colleagues at Yale Cancer Center are taking Harriet?

Kluger We have a group of physicians that meet every other week to discuss cases. The group includes people of multiple disciplines. We mentioned earlier that sometimes the radiologists can tell us whether a tumor is suspicious or not, so we have an excellent

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radiologist, Dr. Gary Israel, who is an integral part of the group and he is excellent at reading these kidney masses and assisting us in deciding whether we should go for surgery or not. Then we have two dedicated pathologists, Dr. Kenneth Haines and Dr. Demetrios Braddock, who help us with doing the molecular subtyping as well as the histologic subtyping, and we will explain in a minute exactly what that is. There are three surgeons who do surgery for kidney cancer, Dr. Dinesh Singh is the laparoscopic expert and Dr. John Colberg does all of the open surgeries, Dr. Edward Uchio actually does both of them, and there are three medical oncologists, Dr. Sznol, Dr. Kelly, and myself. We all get together to discuss cases because sometimes its not clear whether we should try to do systemic therapy, in other words therapy by pill or by IV first to shrink a tumor in order to make it more feasible to resect that tumor, especially if it's a complicated case, or whether the patient is a candidate for surgery. There are all sorts of issues that need to be discussed at this multidisciplinary tumor board and that's where a lot of the action happens in terms of the decision-making. It's very difficult to get five people to give input by telephone at different times, but this forum enables us to have an open discussion about individual cases that are complicated.

Chu Now, would you typically see the patients together in a multidisciplinary clinic or are there plans to do so?

Kluger Yes, there are, and we do sometimes do that if a patient goes into the surgery clinic and needs to see a medical oncologist, often they will page us and we go upstairs to see the patient with the surgeon. Sometimes we do that in a more formal fashion, we have a multidisciplinary clinic on a Thursday morning where we see patients together with the surgeons, and going into the Smilow Center, we will be sharing space with the urologic surgeons and we can discuss patients while they are there.

Chu That would obviously be great for patients so that they don't have to go from clinic to clinic to a different office etc.

Kluger Yes, it makes it much easier for the patient. It all happens in one sitting, although I must admit that it's often a long session for the patient. When they see three or four doctors sometimes they have to be there for a few hours.

Chu Now we were talking about how surgery is the preferred approach for say someone who has a more locally confined disease, but are there any cases in which surgery might not be indicated because of individual patient characteristics?

Kluger Yes, sometimes the patient has other medical problems and if you are going to remove a big

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part of the kidney they may not have enough kidney function to keep going, or if a patient has heart disease or lung disease, they may not be good candidates for surgery. In those situations, we tend not to do it. Sometimes it's more of a technical problem, the location of the tumor in the kidney is what makes it difficult for the surgeon to resect, and those are the perfect patients to present or discuss at our multidisciplinary committee, because then sometimes we give therapy by mouth or intravenously upfront in order to shrink the kidney tumor and makes it much easier for the surgeon to resect that tumor.

Chu Now, is there ever any need for dialysis for patients who have kidney cancer and undergo surgery? Would someone, say for instance, who has chronic renal failure and is receiving dialysis, would that be a contraindication for undergoing surgery?

Kluger We would still remove the kidney in a patient who is on dialysis, certainly if the patient is already on dialysis and they are not using the kidney and a tumor develops in that kidney, we might as well take the kidney out. I think the bigger problem is patient's who are borderline for needing dialysis, and then if you remove a tumor and the area around the tumor, we might actually be removing enough of their healthy kidney to tip them over into needing dialysis, but it does not happen all that often that surgery has pushed someone over into dialysis.

Chu One of the real advances that's been made for kidney cancer is in the treatment of advanced metastatic disease. Can you take us through what has been developing over the last few years?

Kluger Yes, this is a very exciting time to be a kidney cancer oncologist. In the mid 1990's, the first drug was approved for kidney cancer, interleukin-2, and that's very difficult therapy that not everybody can tolerate. The advantage of giving high dose interleukin-2 is that there is a certain percentage of kidney cancer patients whose disease is actually cured by the interleukin-2 and the response rates are in the order of 20%. Yes, it is not very high, but those responses tend to be very-very durable. So, we like to do that as our first therapy.

Chu Can you explain to our listeners what interleukin-2 is? It sounds pretty fancy.

Kluger Yes, it is very fancy. It is a growth factor for a certain type of T-cells and so in essence we are activating the immune system to fight against the kidney cancer. We give it inpatient, and there are a lot of side effects and it's not easy to tolerate, but patient's tend to get through it, we tend to push them very hard even if they are not feeling well, but we hold their hands through the therapy and as I said before, there is a subset that has a very prolonged response

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or remission after the interleukin-2. We tend to try to do that, so that's an immune based therapy.

Chu One of the things I have to say that I have been very impressed with is the way that you folks have been giving the interleukin-2. You have modified the dose and so while there are side effects associated, I was actually at the National Cancer Institute where this interleukin-2 therapy was developed and everyone needed to be in the intensive care unit to be carefully monitored and everyone got really sick, you and your kidney cancer team have modified and tweaked the dosing and patients seem to tolerate it much-much better and seem to have as good, or perhaps even a little bit better, results.

Kluger That's correct, we give the interleukin-2 twice a day rather than three times a day, and we give it on a regular floor. The patients are very carefully monitored, and they are seen by a physician or physician extender before every dose. We have been able to keep about 90% of patients out of the intensive care unit with this fashion. There is a higher nursing to patient ratio, but not as high as in the intensive care unit and our experience on the first patients treated, a few dozen patients, it that appears to be as good as giving it three times a day.

Chu What about these new targeted therapies that have been developed to treat kidney cancer?

Kluger Yes, for the patients who do not respond to interleukin-2, or are not candidates for interleukin-2, there are a number of new therapies that have been developed. As of today, six drugs have been FDA approved in the last few years. I think the first one was FDA approved in late 2004, and since then we have had another five. All of these drugs target what we call the vascular system, or the vascular factory of the tumor. So, these tumors need a lot of blood supply and if you turn that off, it tends to suffocate them and take away the nutrients and then they cannot grow. The first drug to be approved was called sorafenib, the second one is called sunitinib, and then after that we had temsirolimus, everolimus, and then bevacizumab. Most recently we had a drug called Votrient (pazopanib) that was approved just a few days ago. So we now have a list, or a whole armory of drugs that we can use in this disease. None of them really appears to give us the kind of cures that we see with the immune based therapies, but we can keep patients going for a long time. We have patients who had bad disease when we first met them and they have been on these drugs, we just treat them sequentially with one drug after another and we can keep them going for many years with these therapies. We tend to give them sequentially. There have been a number of studies where they have used them together; the toxicity though is quite prohibitive when given together. So, we give them one after the other, now there are other drugs also being

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studied that I would like to mention, and some of them look very promising. There are a number of immune based targeted therapies, we have a study that Dr. Sznol is leading at Yale with an antibody to one of the molecules that essentially puts the breaks on the immune system, so you give this and you activate the immune system and that seems to be working very nicely in kidney cancer and we have other clinical trials.

Chu And what is that drug called, Harriet?

Kluger It's an NtPT1 antibody; it's made by a company called Medarex. Then we have another clinical trial, also of a molecule made by Medarex, and this is a very fancy immune stimulant sort of conjugated to a toxin. We have just started doing this trial and so far patients are tolerating it well, it's a little early in the game to say whether its working or not though. But there are a number of other drugs that are being studied at other institutions, such as a drug called ipilimumab, it's a monoclonal antibody to a different molecule that puts breaks on the immune system and has been proven to be effective in kidney cancer as well as in other diseases.

Chu And are there any attempts to try to combine some of these different immune therapies to try to maximize the immune mediated effects?

Kluger We will be getting there, we are starting to combine them in other diseases, but for kidney cancer we are not that far down the road yet.

Chu Any thoughts about combining the immune therapies with these new targeted therapies? Is there any possibility that might also work to kill the kidney cancers a little bit better?

Kluger There definitely is, and the first step would be to establish the other immune therapies, the other targeted immune therapies for kidney cancer, and then add other drugs. Again, we are not there yet for kidney cancer, but we will be getting there I am sure down the road, because presumably if you target the immune system and the blood vessel manufacturing, you might not have overlying toxicities and it may be easier to administer those drugs in combination rather then giving a combination of two drugs that target the same thing.

Chu I guess one of the advantages of these new targeted therapies is that some of them, or many of them, are actually oral, so patients don't necessarily need to be admitted to the hospital or get intravenous injections.

Kluger Yes, that is an advantage, although we do warn patient's that just because something is given as a pill it doesn't mean that it is better tolerated than something that's given intravenously,

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and in fact, our experience with the kidney cancer drugs is that the less toxic ones are the bevacizumab and the temsirolimus that are given intravenously, and sunitinib, which is given by pill is often not well tolerated, but all of this is individual and there are patients who tolerate the pills very well and patients that don't.

Chu In closing Harriet, we just have about 30 seconds left, any messages that you would like to give to our listeners out there this evening about kidney cancer?

Kluger I would say that it's no longer a hopeless disease as it was five or six years ago when we only had one drug, interleukin-2, we now have a lot to offer. I would suggest that they try some of these immune based clinical trials as well because those actually offer a lot of hope for more durable remissions.

Chu You have been listening to Yale Cancer Center Answers. I would like to thank my guest this evening, Dr. Harriet Kluger, for discussing the treatment in the detection of kidney cancer. From Yale Cancer Center this is Ed Chu wishing you a safe and healthy week.

If you have any questions or would like to share your comments, you can go to yalecancercenter.org, where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.