

Yale CANCER CENTER

answers

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Prostate and Urologic Cancers

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven, Dr. Higgins is professor of Therapeutic Radiology and of Obstetrics Gynecology and Reproductive Sciences, and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert in myelodysplastic syndromes. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you could submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. Tonight you will hear a conversation about prostate and urologic cancers with Dr. Michael Hurwitz. Dr. Hurwitz is Associate Professor of Medicine in the section of Medical Oncology at Yale School of Medicine. Here is Dr. Susan Higgins.

Higgins Why don't we start off with talking about how you got interested in this field?

Hurwitz I actually became interested in oncology while in college because I was studying biochemistry and we were learning about cell biology and someone randomly gave a lecture on oncology and it was so much more interesting than any of the other stuff and I immediately was interested in it. Then, after med school, I was aiming to do oncology and then urologic oncology, that wasn't until later, but the diseases are very interesting, and the patient populations are people I am interested in dealing with. I think there are lots of different types of oncology I could be interested in, but I think urologic is particularly interesting because it is a wide range of diseases, there is prostate, which is all male, there is bladder which is more of a mix and there is kidney which is more of mix, and the biology is very different for all of them, the treatments are very different for all of them, and it is just a very interesting field for that reason I think.

Higgins In previous shows, Steve and I were discussing that people don't realize that even though you are a medical oncologist with a subspecialized interest in urologic cancers, there is so much within that group. Maybe you can expand upon that because people hear about prostate cancer all the time, but when we talk about urologic cancers, it is sort of a family of cancers right?

Hurwitz Yeah, absolutely. Again, starting with prostate, this is the most common, so that is a disease that again obviously only affects men because only men have a prostate. And that's a little unusual in cancers because there are really 2-3 different classes of it. There is the prostate cancer that almost every man will eventually get. By the time men reach 80 in America, probably 75% of them have some cancer; most of that is irrelevant, it is never going to go anywhere, not going to be a problem, but then there is a small group within that, where it is a real problem where it can even kill you and that's why prostate cancer is the fourth leading cause of death amongst cancers in America. It is a very interesting disease because there is a broad range of presentation and a broad range of once it does present, how it is going to affect you. Bladder cancer is not as common, but what people don't know probably is that it is one of the most expensive cancers in America because it turns out that with bladder cancer, at least half the time, or about half the time, if you develop one and even if they take it out, you will develop

more within the bladder, and because of that, people who get an early stage bladder cancer, which we can cure just by taking it out, and when I say we, it's not

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me, it is a urologist, those people have to get screened with looking into the bladder with a scope, kind of like a colonoscopy, but it is a cystoscopy into the bladder every 3 months forever, and so that has its own challenges. And kidney cancers are in a totally different class, and we use to not discover them that often. Now, we discover them a lot more because that is another disease where a lot of the time it is not that significant, it is growing slowly and not doing much, and you get a stomachache because you have been eating too much Chipotle or something, and they get to a CAT scan, and find something in your kidney. That also has very different challenges and treatments, and kidney cancer, unlike most cancers, really isn't treated with chemotherapy. And the one I didn't mention that is also frequent, is testicular cancer, which is again only males and it is also much more common amongst very young people, teens and young men. So, it is a very different population, mostly curable, which is great, but again, very different.

Higgins Going back to prostate cancer, you alluded to one of the really fascinating parts of prostate cancer, which is that there is a whole range in terms of the characteristics or severity of disease and for some men, prostate cancer is going to be maybe a chronic disease that they live with, that never affects their lifespan and for other men it will be a much more significant health problem. Could you give the listeners a sense of why that is?

Hurwitz It's a really important point for patients because while I say that, there is a large population where it doesn't matter that much, I will get into that; there is a small population where it is really significant and it can grow very fast and be deadly, then there is sort of a middle ground where you are going to have to treat it, but people can live a very long time, and there is a lot on the web out there about all these different groups and it is very hard for the patients to figure out where they stand. I have patients who come in with a prostate cancer that we know is very unlikely to affect their life at all and they could ignore it, but they want extremely aggressive treatment because they read the stuff on the web about people with advanced cancer who are dying of it, and then you have people coming in who already have advanced cancer that has spread to other parts of the body, we know it's going to be extremely dangerous for them, and they don't want to do anything because they have read the stuff on the web saying everybody has got prostate cancer. So, going back to what you asked, the prostate is a little organ that sits underneath the bladder. The urethra goes through it, and so urination goes through it and a lot of men have prostates that get larger with age and they have problems urinating and that is not cancer, that is usually called benign prostatic hypertrophy, but prostate cancer apparently develops sort of as normal aging, at least in American men, and as I said, by the time you are 50, probably a third to a half of men have a little bit of prostate cancer and then by the time you

are 80, three-quarters of men do. And most of that won't ever do anything, it is cancer based on the fact that under a microscope when we look at it, it's cancer the cells are growing abnormally, but they are never going to go anywhere. And we do have ways of testing whether they are likely to go anywhere or not. It is not perfect, but we have a pretty good idea for a lot of these. Then, there are the ones that you look at under the microscope, and they are aggressive. Maybe they have already spread a little bit outside of the prostate through something called the prostate capsule. These are ones that we know will be more aggressive and they need to be treated with either surgery, or you can use radiation to treat them, and the other

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thing that I didn't mention but it is very important is that prostate cancers, prostate cancers and prostate tissue depends on something to grow. In fact, every cell in the body depends on something to grow. If you take human cells out of the body, they just die on their own unless you give them something called a growth factor. And the growth factor for prostate cancer is something called testosterone, which is very similar say for example in breast cancer, women need estrogen for a lot of their tumors to grow. So, often we try to remove testosterone from men; basically, we can chemically remove it. And a lot of people have to be on those medications for many years because we know that without them, the prostate cancer will grow.

Higgins It is so interesting that you mentioned that because I think a lot of people are not familiar with this idea of what we call androgen deprivation as an actual therapy that is targeting the prostate cancer and it's a very interesting part of what you do, maybe you can just describe what androgen deprivation is about.

Hurwitz It goes back to this idea that every cell in the body needs something to survive. It is very important for cells in the body not to be free agents, you don't want them dividing on their own. It's a very, very bad idea, and it's not that big a deal as we have so many cells if one or two die, but if they live when they are not supposed to, that's an issue. The primary thing that tells prostate cells to survive is the stuff called testosterone or androgen. Androgen and testosterone, we use the term relatively interchangeably. And most of it is made by the testicles, and the brain actually sends out signals that eventually lead the testicles to making testosterone. We know that prostate cancer cells, because they originally were prostate cells, have gone wrong. They too are usually dependent upon testosterone, occasionally they are not, but for the most part, they are. And therefore, if you remove testosterone from the body, they will shrink and many of them won't grow for a long, long time, and the way we do that is basically we send out signals, sort of like the brain does to tell the testicles to stop making it. And we usually use a medication called leuprolide, there are some other ones like that. And then there are some other pills that we use that people may have heard of, called Casodex or bicalutamide, those work a

little differently but they also prevent the testosterone from telling the cells to divide and grow. And then there are newer therapies that if you are hearing about prostate cancer you will know from the web that are more effective than the pills. There are newer type pills that are stronger, and one of them works to decrease the amounts of testosterone and one of them works to block the testosterone from working where it normally works.

Higgins In the management of prostate cancer, one of the things that has fascinated me is there is a little bit of art and a little bit of science. When you meet with patients, I know as a radiation oncologist, earlier in my career, when I had to spend time discussing prostate cancer and this concept of watchful watching, we are talking about therapies, but then there is this concept of watchful waiting, and it is a little bit not in keeping with everyone's idea of how we manage cancer, we actually don't treat it, but we monitor, maybe you can talk a little bit about that watchful waiting process?

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Hurwitz Yes, and we have changed the name. I'm glad that you brought it up because we try not to use that term because it implies that we are just waiting and not doing anything. We have changed the name to active observation or active surveillance, and it is active because what we are really doing is, again there are criteria that we use to decide whether it's likely that a prostate cancer is going to grow and cause problems. And the criteria that we use are we look at where it is in the prostate, and the way we do this is by a biopsy. Unlike a lot of cancers, it is not so easy to find prostate cancer within the prostate. We are better at it now because we can use MRI testing. That is still somewhat experimental. They are doing a lot of that at Yale in fact. There is a doctor named Preston Sprenkle, who is one of our urologists who does a lot of that. But by our standard methods, you can't really tell where in the prostate the cancer is. So when you get a prostate biopsy, they randomly biopsy different parts of it. You may be asking, why do you get a prostate biopsy in the first place? And the answer is, usually you get a PSA test, which we didn't get into, but is probably worth talking about. PSA is a thing produced by prostate cells and usually at higher levels by prostate cancer cells that you can find in the blood. And if your PSA is rising, it is often an indication that there is prostate cancer. For most patients, you get a PSA test. It shows it is elevated and then we will do a prostate biopsy and that prostate biopsy will look all over the prostate. They will do 12 different little chunks of the prostate and then a pathologist looks at them under the microscope. And then what we do is, we use a combination of just how high that PSA test is, how many of those biopsies had tumor in them and what the tumor looks like. So, we have pathologists who will look at the tumor under a microscope and say, this looks aggressive or this doesn't aggressive. And then the combination of those things can tell us often whether this thing is likely to spread or not. And when it looks like it is not likely to spread at all, then we often do this thing where we say, here is what we are going to do, we are going to observe you but actively, we are going to keep checking PSAs, we are probably

going to biopsy you again in a year or two but we are not going to treat you, and the reason has to do with the idea that 80% of men, 75% of men who are 80 years old have this and the vast majority of them, they are not going to suffer from prostate cancer and the treatments that we do are not benign; so, either surgery or radiation, both have a fair number of side effects, and we really want to avoid those if there is no reason to do that.

Higgins Thanks so much for that. I can't wait until we get back to our discussion. But right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about prostate and urologic cancers with Dr. Michael Hurwitz.

*Medical
Minute*

There are over 13 million cancer survivors in the United States and over a 100,000 here in Connecticut. Completing treatment is an exciting milestone, but cancer and its treatment can be a life-changing experience. Following treatment, cancer survivors can face several long-term side effects of cancer, 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 to help keep cancer survivors focussed on healthy living. The

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Survivorship Clinic at Yale Cancer Center focuses on providing guidance and direction to empower survivors to maximize their health, quality of life and longevity. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale- New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR, Connecticut's public media source for news and ideas.

Higgins Welcome back to Yale Cancer Center Answers. This is Dr. Susan Higgins and I am here with my guest Dr. Michael Hurwitz talking about prostate and urologic cancers. Maybe we could start off talking about the team approach, because I think what we as oncologists now feel is the standard of care is to have multidisciplinary tumor boards where we discuss a patient's case and then decide on a game plan and it's really a large number of people that are behind the scenes that patients don't even see who are working on their behalf to put together their treatment plan, and I thought maybe you could tell us a little bit about that.

Hurwitz I totally agree the team approach is vitally important and the components that you alluded. To start you see a medical oncologist, who often isn't the starting point at all in urologic malignancies. So there is going to be a medical oncologist, there is going to be a radiation oncologist and again, for example, in prostate cancer they are central to treatment of disease that hasn't yet spread and for people who need palliation, and that is also true for renal cell

carcinoma and for bladder cancer and for certain types of testicular, so radiation is vitally important. There are surgeons, in our case the urologist, but that it can also be lots of other types of surgeons; for example, there are patients who require complex surgeries and they will have a urologist, if it is metastatic cancer to the liver, we will have a liver specialist, and we will have vascular specialists. And then we have the radiologists, who are unbelievably important because they can tell us where lesions are, they can tell us if lesions are changing, they are vital, and last but certainly not least are the pathologists, and these are the guys who actually tell us what we are looking at. With cancer, you can see a mass on the CAT scan, you can take the mass out, but unless you know what it looks like under the microscope, you don't know what you are treating, and pathology has become much more than that of course because they are also looking at the molecular details of these cancers, which in modern practice completely changes what you do. So, it's really five groups at the baseline for multidisciplinary care, and we have our tumor board every week and we have lots of cases and often the community can bring cases in too.

Higgins I like the fact that you mentioned the pathologists because we know not all prostate cancer cells are created equally and when people read about it on the internet when they look at the words prostate cancer, up comes Gleason grade, and it is a rather complex notion for a person who is not a pathologist, maybe could you just talk about that a little bit.

Hurwitz The Gleason grade is a great example of why you need pathologists who really know what they are doing, which is not so easy. A pathologist, Gleason, came up with it and basically when he looked into the microscope of prostate cancers he said, okay I notice that there are 5 different levels of badness in cancer, that is, level 1 which looks a little bit bad and there is level 5 which looks

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demonic, just terrible, terrible cancer. And what he did was, he said, when I look at all the cancer that I see in all the biopsy specimens, I am going to say what the most common of those is; like I see a lot of level 3, then we will call it a 3. Then, if I see the second most common, that is a level 4, then we will call that a 3+4. Gleason grading goes from 2-10. So, in theory, you could have all one, so a 1+1 is a 2 or you could have all 5, 5+5 is 10. What we use nowadays is we call cancer 3+3 or greater. So, Gleason grading goes from 6-10, 3+3 up to 5+5. Anything 3+3 is good for the most part, and if it's localized in the prostate, that's good risk and 7, 3+4 or 4+3, are in the intermediate range, and anything more than that is pretty high risk.

Higgins I think that the average person doesn't even realize perhaps that there are so many different subspecialties even within pathology and I know from treating gynecologic malignancies for many, many years that the people who do it more, do it better, because there is a lot of nuance and actually I am on the NCCN panel for gynecologic cancers and on these national guidelines,

we are actually now including at the beginning of the decision tree, get an expert pathologist and there are certain areas we would agree as oncologists like prostate, sarcoma, lymphoma, gynecologic malignancies, where people who are at what we would consider a high volume center, where they see a lot of this, are going to have more expertise to offer and experience to lend to that process. I am really glad you discussed the pathologist, who is behind the scenes and doesn't see the patient, but again, in our multidisciplinary setting is a core member of the team. And the other person, the imaging people, again a similar concept, people who do more of this type of imaging, especially the highly specialized MRIs that we were just discussing are really sub, subspecialists who have a very particular expertise. Could you discuss the MRI and how it's working into the equation now?

Hurwitz Firstly, I couldn't agree more with all that, I have to stay that I lecture med students sometimes and I explain to them that I was the worst pathology med student on the planet and now I am completely and utterly dependent upon them, they are the most important people in my life. So, the MRI though is something sort of new in prostate cancer. PSA testing is quite controversial now. And I think that the data are more and more coming out on the side of PSA testing should absolutely be offered to patients. They don't have to take it, but I think that the data are quite convincing. That's my opinion, and I think that's the general opinion of most medical oncologists who do this and most urologists who do this. And I didn't mention, by the way, there are also newer urine tests that look for molecular changes in the prostate that might also help with this. So, we have gotten into the 21st century.

Higgins Again moving in that direction of personalized medicine.

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Hurwitz That's true also, yes.

Higgins Let's figure out who needs the treatment, how much, and specifically what type on an individual basis. And in that direction, the personalized medicine specific-targeted therapies, I was wondering if you could just give us your view on what are the more exciting and important developments happening on the forefront in the frontiers of research in your area.

Hurwitz I think that in bladder cancer and kidney cancer, there are some very exciting things happening. Bladder cancer is a disease that again is not as common, not as well known to people. A lot of it can be cured if caught locally, but if not, it is really uniformly lethal. There is almost no survival if it has spread, much like lung cancer and pancreatic cancer, and we have chemotherapy that can often shrink the tumors, but it does not work forever. And we have not had any new treatments really in about 10 years at least. Over the last year or two, some really

exciting things have come out using the immune system to attack, and this has been shown to work for a lot of patients. Specifically, there was a medication, I think it has a name now, but it was called NPD3280A, and it was a medication, an antibody, that when infused into people would basically turn on T-cells, part of the immune system that were not activated, and allow them to attack the cancer, and in patients who had certain molecular details of their cancers, they expressed something called PDL1 at high levels on their cancer cells, those patients, I think over half of them would have tumor shrinkage and some of that could last a very, very long time, and that's the first really big advance in many years, and I'm hoping that it's going to be an advance that will continue on. And in kidney cancer, the same sort of thing. We are seeing very exciting results with therapies aimed at these same exact mechanisms.

Higgins I think we all agree that the immunotherapies which are now being used with great success in melanoma are really some of the most exciting therapies that we have seen in many years. It's great to hear that we will be able to offer those, and do you have trials right now that are running with those immunotherapies?

Hurwitz Yes. In bladder right now, we actually don't, but we have in our phase 1 group of immunotherapies, and so with bladder cancer, sometimes you can get into the phase 1 trials. In kidney cancer, we do. We have two trials open right now for early stage.

Higgins And what about side effects? What are you seeing with the immunotherapies in general? What kind of side effects do people have?

Hurwitz The immune side effects that you see are sort of what we would expect because you are activating the immune system in a way that is not normally activated. Backtracking a little bit about why these things work at all, every time that you get a cut, your immune system turns on in that area because you have foreign stuff getting in. The immune system is supposed to prevent that foreign stuff from causing infections, and that's fine. But at some point, you want to turn it off, right? If you get too much of this stuff, you get inflammation everywhere and that can cause what's called

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autoimmunity where your own cells get attacked. And it turns out that cancers sort of use the fact that we automatically turn things off, to turn off the immune system from attacking them. And what we are doing with these medications, this new class of drugs that are called immune checkpoint inhibitors, is doing exactly that, we are turning off that brake, and it's great because it attacks the cancer cells, but you get autoimmunity. Now, most people don't actually, but depending on the therapies between 10 and 20% of people do. The most common side effects are something called immune colitis where the colon is attacked and people get bad diarrhea,

sometimes even bleeding and often have to go into the hospital, and we have to give them steroids which sort of calms down the immune system for a certain amount of time. That's probably the most common one. Other common ones are thyroiditis, so the thyroid can get attacked, you could become hypothyroid, which again is very common in the population and that's you can basically give people thyroid hormone, which protects them against that. Pneumonitis, which is lung. The lung can get attacked and you can have difficulty breathing and you can get fibrosis, fibrous stuff coming in the lungs and that could be very serious. That's relatively rare, but it can happen. And then sort of any other thing you can imagine has happened, any immune attack, so you can get diabetes if the pancreas is attacked, you can get muscle aches and other things like that. It is really anything that looks like autoimmune disease.

Higgins And so we talked about these trials, I know you are running the phase 1 trial, how do people even find out about these trials?

Hurwitz I would say the best way to find out about trials is to call. If you have a cancer, call, reach somebody and we will figure out if there are trials available for you. One thing that I would like to tell patients about is that there is a website called *clinicaltrials.gov*, it's from the US government and it is any trial that is happening in America, and in a lot of places in the world, and they have to tell the *clinicaltrials.gov* people that the trial is open, otherwise the trial is not, I don't know if it is not legal, but it won't be used. So, anything available will be on that website, and within that website, you can ask for trials in Connecticut, and you can look at them in other states. So, that's a pretty easy to find out about diseases and if there is a trial available for that disease.

Higgins And that's *clinicaltrials.gov*?

Hurwitz That's right.

Dr. Michael Hurwitz is Associate Professor of Medicine in the section of Medical Oncology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC, and as an additional resource archive programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.