Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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Minimally Invasive Treatment for Prostate Cancer

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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 and Dr. Chagpar are joined by Dr. Peter Schulam. Dr. Schulam is Professor of Urology, Chair of the Department of Urology and Chief of the Department of Urology at Yale-New Haven Hospital. Here is Francine Foss.

Foss Could you start us off by telling us a little about yourself, you are new to Yale, so tell us where you came from and about your background.

Schulam I arrived here in January from UCLA where I was for the past 11 years. I did my surgical training at Johns Hopkins and my urologic training there as well. From there I had a short stint at Baylor College of Medicine in Houston and then out to UCLA where I was for the past 11 years where I was Chief of Minimally Invasive Surgery for Urology and also Vice Chairman for the Department.

Foss Why don't we start right in with the hot topic which is screening for prostate cancer and PSA. There has been a lot of controversy about that in the media recently, what is the real scope?

Schulam Back in October or November, the US Preventive Services Task Force published an initial report, not the final report, giving PSA screening a D rating, and what that stands for essentially is that they found that PSA screening is ineffective or that the harms outweigh the benefits. In May of this past year, they reported their final recommendation and that basically did not change. They gave PSA screening a D rating, and this has created quite a bit of controversy because everyone is now confused, should I get tested for PSA? Should I look for prostate cancer? What is the purpose of screening? And I think in order to fully understand that we have to take a step back and try to understand why the U.S. Preventive Task Force would make that recommendation. Going back to the definition, they were looking at whether the harms outweigh the benefits, so what are the harms of actual treatment? And the question is what happens when someone undergoes treatment for prostate cancer? Well there are two ways to be treated, one is radiation and the other is surgery and both of them can be associated with morbidity or long-term consequences. With surgery the long-term consequences have to do with incontinence, the ability to control urinary stream and potency, and the ability to have a normal erection for intercourse. With radiation therapy, incontinence is not as significant, however, sexual dysfunction is and there are also issues regarding proctitis and cystitis and these are conditions that affect both one's bowel movements and also one's ability to empty their bladder. Because of that, and with the feeling that the benefits were not as great as those, that was what the recommendation was based on.

Foss Can you tell us a little bit about how we connect up the PSA with these invasive procedures? Take us through how the PSA was used.

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Schulam In screening for prostate cancer, in order to detect prostate cancer there are two techniques that are used, one is a digital rectal exam, so you actually palpate the prostate and you are essentially feeling for a lump or hardness in the prostate and the other is you test someone's serum, or a blood test for PSA, and PSA stands for prostate specific antigen and it is unfortunately not specific for cancer, so everyone has a PSA, the question is how high the PSA is, and there are three causes of why a PSA would be elevated, one is infection, one is just regular tissue in the gland as the gland gets bigger, or benign prostatic hypertrophy, and the other is cancer. So unfortunately, not having a specific marker, the way we diagnose prostate cancer is we do both a digital rectal exam and check the PSA usually beginning around age 50, and in those gentleman with a family history, we may begin as early as 40, and if either one of those are abnormal, that would then warrant a biopsy. So that's how the diagnosis of prostate cancer is made.

Chagpar So despite the USPSTF recommendation, you are still recommending PSA so that we can detect prostate cancer earlier?

Schulam Here is the issue, the question should be, is prostate cancer dangerous? And if so, how can we prevent that danger from arising in the public? And the bottom line is that in 2012, it is estimated that over 240,000 men will be diagnosed with prostate cancer in the United States and 28,000 men with prostate cancer essentially die from prostate cancer, so knowing that there is a significant risk associated with prostate cancer, how then do we determine who we should treat? The biggest change and what the Task Force is asking us to look, is there is no doubt that in the United States over the past few decades we have probably over treated prostate cancer. In the past, we have screened to treat, meaning if we found any prostate cancer, we took out your prostate and provided you with radiation therapy, now we understand that probably we should screen to detect and then of those where we detect a prostate cancer we can determine who needs to be treated, so there is one additional step that we need to carry out and I think this is our call moving forward in the future, is to move away from screening to treat, but screen to detect and then determine those patients who would most benefit from treatment because undoubtedly we are going to have 240,000 diagnoses, and 28,000 deaths attributed to prostate cancer, the question is, who would benefit from treatment rather than just treating everybody, and that is what we have to do I think moving forward.

Foss With this recommendation to not obtain the PSA, is that going to impact payers? Is our insurance company going to pay for this, is Medicare going to pay for this? How is it going to impact the individual?

Schulam Well a similar thing happened for mammography and there was actually a movement by the insurance companies to not pay for mammograms, eventually the government stepped in and actually changed that ruling. I do not think this is going to impact insurance or reimbursement for PSA testing.

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Foss Let's go back to what you were talking about before, about screen to detect, how is it that you make the decision about which patients really do need treatment and in which patients you can pursue watchful waiting?

Schulam That is a great question. What is interesting about prostate cancer is it is the only solid organ in which when go to biopsy, we cannot detect any suspicious areas. So we actually just do a random biopsy of the prostate. I want to take a step back because I think this is important for everyone to understand, once the decision is made that we want to rule out cancer based on a PSA or digital rectal exam, the next step is a biopsy usually performed transrectally. It is an outpatient procedure. Again, this was also considered a part of the U.S. Preventive Task Force that there can be side effects or complications associated with a biopsy, it is not completely benign and the most common is infection, but barring that, this is our next step, because we cannot image prostate cancer because prostate cancer and benign prostatic hypertrophy, or normal prostate tissue, do not look very different on a CT, MRI or ultrasound, what we end up doing is basically using an ultrasound just to identify where the prostate is, and then we randomly detect on average twelve cores hoping that we hit the area that would contain cancer if we want to make the diagnosis, so you can understand that in the biopsy process alone in which we are diagnosing prostate cancer, we can have individuals in which we have a negative biopsy, but in fact they have cancer or we can have someone who has prostate cancer but we do not know the exact extent of prostate cancer, or we can actually make the diagnosis, so there is a lot of ambiguity there alone. Once we have the biopsy, what happens is the pathologist looks at these cores of tissue that we have obtained under the microscope and they grade the tissue from one to five. All we look at is architecture and it is essentially like looking at a cobblestone street. If everything looks ordered, no cancer, everything is fine. As the disorder increases, it gets graded from one to five and so one would be mild disarray, five being the most amount of disarray. What the pathologist also does is because now most people will say I was told that I have Gleason grade three plus three. They will pick the most predominant area in the core and then look for the second most predominant area, grade each one of those individually from one to five so you get a sum score. So people will present saying, I was told that I have Gleason 3+3, I have Gleason 4+4 and you would ask why would that matter. Where it does matter is the more high grade cancer you have, the more concern we have that you could have an aggressive form of cancer that should be treated, and so at Gleason 7, the first question you ask yourself is, is it 4+3 or 3 +4, because 4+3 would indicate that you have more Gleason 4 in your biopsy than Gleason 3, where as Gleason 3+4, we have more Gleason 3. We are now beginning to feel that if someone has a low volume of Gleason 3+3, so they have Gleason 6 disease, these may be individuals who may benefit from active surveillance, that is we watch them closely, so the areas that we need to get better at in the future, going back to your question when you said screen to detect versus screen to treat, once we have detected prostate cancer, how can we identify those who would benefit? Right now we are basing it on a random biopsy, which needs to change. We are basing it on our inability to actually image prostate cancer and we do not have the genetic markers that can better distinguish or differentiate very aggressive cancers from more indolent cancers. So determining those that should be treated versus those that should not and

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those are the areas, for instance here at Yale, that we are working on. Probably the next iterations in our process here is once we have diagnosed someone with having prostate cancer and we want to determine whether they are a reasonable candidate for active surveillance, we now are working with the radiologists here. There is a particular type of MRI called the multiparametric MRI, essentially that just means there are three different phases of MRI scanning that is done to the prostate and by combining those three we are beginning to be able to differentiate cancer from noncancer. So now we might be able to indentify a suspicious lesion, unlike before we were not able to see prostate cancer, we might be able to see it. Now the question is can we go ahead and biopsy that area? The problem with MRI is that there are ferromagnetic limitations. You cannot bring anything metallic into the MRI scanner, so it makes biopsying under MRI guidance a little bit more challenging, so what we are beginning to do now, there are tools and techniques and companies working on being able to develop products that will allow us to biopsy under MRI guidance, but it is a little bit cumbersome. We are working with a company and they have a device called the Artemis device and this is very unique. What it allows us to do is obtain a multiparametric MRI on a gentleman who either has suspicion of cancer or in fact has cancer. On a work station, we can look at the MRI and identify and actually encircle areas or regions of interest, areas that we think are highly suspicious of cancer. We can bring the patient into our clinic, perform a transrectal ultrasound with the Artemis device, which has a robotic arm attached that allows us to scan the prostate and get a three dimensional recreation of the prostate and then the work station or the computer with this device takes the MRI that we had previously acquired and fuses it with the 3D real-time ultrasound. So now while driving the ultrasound, I actually can see the areas that are suspicious by MRI and we can do targeted biopsies, so I think these are the programs that we need to move forward, to be able to move from screening to treat, to screening to detect and then determining who we should be treating.

Chagpar We are going to take a short break for a medical minute. Please stay tuned to learn more information about prostate cancer with our guest Dr. Peter Schulam.

Medical Minute *There are over 12 million cancer survivors in the United States right now and the numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and cancer survivors face other 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 such as the one at Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*

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Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my co-host Dr. Francine Foss and our guest Dr. Peter Schulam. We are discussing all kinds of things with respect to prostate cancer. Right before the break you were telling us about some novel technology fusing ultrasound with MRI that is helping us to guide biopsies and helping us make the distinction between not only who has cancer and who does not, but who potentially needs treatment and who we could watch closely. Tell us a little bit more about other advances that you see coming down the pike both in terms of management as well as some of the things that you are doing here at Yale in terms of clinical trials.

Schulam If we break it down, number one we need to be able to image prostate cancer. We have to be able to see it, because if we want to follow somebody for active surveillance, we want to know where the lesion is, if the lesion is growing and we want to be able to target the biopsy. We are moving down that front. The next thing is once we have the tissue, I think we need to have better resolution beyond Gleason grading. This is where I think understanding the genomics of the disease and being able to do sequencing on the tissue is important, which again is another area that is a strength at Yale that we want to explore. We want to be able to have a better understanding of the type of disease. I think right now, Gleason grading from 1 to 5 is fine, but it is a very coarse resolution and I think genomic investigation will provide us a finer resolution to be able to determine who should be treated and who should not be treated. Again, we are on precipice of this new era that we can go into moving from architecture to more what is happening at the gene level. Once we diagnose those with prostate cancer, how should we treat them? Right now, our predominant methods are radiotherapy and surgery and we all talk about robotic surgery, we have to realize that robotic surgery is just another iteration of surgery. It is still a radical procedure. It is still invasive. It is less invasive, and perhaps the complications, blood loss, things of that nature are less, but it is still an invasive procedure with associated morbidity and an associated learning curve. What would be ideal is if we could treat men with prostate cancer and minimize completely the morbidity associated with treatment and the next area of study is the idea of focal therapy. If we can see the cancer and we know there is a predominant lesion in the left lobe, why do we have to remove the whole prostate? Can't we go ahead and just treat that lesion or treat that lobe of the prostate? Unfortunately, prostate cancer can be multifocal, so this all has to be balanced, this is a work in progress, but this scenario is very exciting and then the question is how do you do focal therapy? There is high frequency ultrasound that is called HIFU. Can we develop other techniques to do this? I just came back from the University College of London, where we have collaboration and we are going to work with the department of urology there where they happen to be very active in programs with active surveillance and MRI imaging and focal therapy. Hopefully we can learn a bit from their experience and what we really want to begin to do is have better contrast agents to detect prostate cancer. We are working with the bioengineers here at Yale to potentially incorporate nanoparticles and iron oxide and come up with novel ways that on a cellular level we can identify, using MRI imaging perhaps, single cell of disease, but more importantly what would be great is if we can link that with therapy. So, it would be theranostic, so

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essentially can we go ahead and what we are using to image, can we also treat? This is now a little bit out there and kind of sci-fi, but imagine being able to take a nanoparticle with something in it and it can be honed directly to a prostate cancer cell. It allows us to image the prostate cancer cell. It is no where else in the body but in that and then imagine putting that patient in a device, our thought process is perhaps if we have iron oxide we can do something like inductive heating, very similar to what you have in your home stove, so with a magnetic field, you can activate what is now inside the cell and heat that cell and actually destroy that cell without destroying anything else around it. To me that would be the future. The idea would be almost as if we are doing surgery not from the outside in like we do today, but from the inside out with minimal bystander effects. The idea would be the capsule of the prostate, the nerves, everything responsible for continence and potency would all remain intact and we can treat prostate cancer. Interestingly, the organ itself even though it is a reproductive organ, for most men who are now beyond those years, there is really no utility to the prostate itself and it is a potential source of cancer. The problem is it is so intimately associated with functional processes like continence and potency that what we really want to do is figure out, is there a way to treat it 100% of the time without affecting the nerves and muscles in the area so that we can maintain continence and potency? I think that is truly the future and those are the areas that we want to work on and I think that is where the most excitement lies.

Foss Peter, you talked about the new robotic techniques, can you tell us if that is available in all centers or is that a specialized procedure that a person would have to come to a cancer center for? In other words, if a person presents in a community hospital, what is the approach going to be and how different is it going to be and what are the advantages of coming to a specialized center?

Schulam Interestingly, over the last decade, prostate cancer surgery has evolved from open surgery to laparoscopic, to robotic surgery and I would say that in the United States now, please do not hold me to it, but somewhere on the upwards of 80% to 90% of all prostate surgery in the United States is performed with a robot. And so that would be both in the community and at academic or large speciality centers. I think the most important thing in selecting a surgeon for prostate cancer is not only experience, but the relationship that you have with them. Obviously, there is a learning curve, but we have all seen it in prostate surgery, unlike most other surgeries, is the most difficult to perform because not only are we trying to remove the organ, we are trying to maintain function, again continence and potency and even in the best hands, it is not 100% for all three, meaning, successful removal of the cancer, maintenance of potency and maintenance of continence. I think it is important to identify centers and surgeons that you are comfortable with, that have experience with the robot and you really want to know what their personal experience is because just asking someone how many cases they have done is not necessarily good enough, because even among surgeons that we would consider high volume, you can have disparity with respect to their outcomes. It becomes a little more challenging and this is where we as a field of medicine and certainly in my area of interest in minimally invasive surgery and engineering, is where we have to tighten that band up. The bottom line is when we get on a plane, we expect that that plane is going

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land and what we have to do with surgeries, we have to develop tools and techniques that will allow the majority of surgeons performing a particular technique or procedure to operate within a very narrow bandwidth of outcome, which unfortunately does not exist yet and prostate cancer is one of them because it is not just about removing the organ, and that makes this procedure a little bit more challenging than many of the others that we deal with on a daily basis.

Chagpar It seems to me that perhaps in addition to looking at experience and does this person do robotic surgery and am I comfortable with them, one of the things that strikes me is when you were talking about targeting cancers from the inside out and this whole idea of imaging with the latest technology, I would think that kind of futuristic thinking, while we talk about it being kind of like sci-fi, now is really cutting edge that larger academic centers like your's is leading the way on and so to get that kind of therapy, I would imagine that that is not available in every small center.

Schulam There are very few centers that have the capabilities to approach these medical and surgical questions with the resources that are required to answer them. I am fortunate to be here and in my short time I have identified immediately with the school of engineering, I am dealing with the medical school and genetics and we are dealing with the hospital itself trying to put together pathways of treatment. So, because of these resources that are made available, not to mention collaborations with the University of College London , another area that I can gain further experience with, it is allowing us to tackle these problems in real time. When we will have the solutions, it is hard to say, but at least from moving towards that sci-fi solution.

Foss It is sounds like a multifaceted and multidisciplinary program in urologic cancers here at Yale. Could you say a little bit about genetics and engineering, you talked about it a little, but on the flip side of it with what patients are seeing, can you talk about the multidisciplinary team?

Schulam We are very fortunate here. Since I have been here we have recruited three people that are coming in; two are surgeons and one is a medical oncologist, Dr. Daniel Petrylak. I think what everyone has to understand and what I am now trying to build here as a foundation is that the treatment of prostate cancer, bladder cancer, kidney cancer, is a multidisciplinary approach. We need great radiation oncologists, we need great diagnostic radiologists, we need medical oncologists, we need surgeons, and then if we want to do the research, we need the building blocks for research, we need genetics, we need pathology, we need molecular pathologists, and then for my area, trying to look at instrumentation and devices, we need engineering. Fortunately here at Yale, I have all of those foundations to work with. We already have good people in place at each of those areas. I am now currently trying to build and augment all those so that we have the breadth and depth necessary to begin to really focus not on just prostate cancer, but kidney cancer and bladder cancer with the same level of intensity that we are now approaching prostate cancer.

Chagpar Peter, we were talking earlier in the show about the different modalities for treating prostate cancer and it seems like this is really evolving, but one of the things we talked about was watchful waiting

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or careful observation. If I was a guy who had prostate cancer, I might come up to you and say, look I do not want to have prostate cancer anymore, can you get rid of it and I do not want any watchful waiting, do you hear that a lot?

Schulam You raised two interesting points, one is we do not call it watchful waiting, we call it active surveillance.

Chagpar Okay.

Schulam You are not walking away from it. We are following you, we are r re- biopsying you. We are determining if there is change in grade or volume of prostate cancer with time. If there is then we would move you to a treatment arm and not back into the active surveillance arm. And this is where we are really going to need genetic understanding of Gleason 3, and see what differentiates Gleason 3 from Gleason 4 and 5. We really believe that Gleason 4 and 5 are more aggressive cancers than Gleason 3 and in fact you see this in many other diseases. You have something that really is not cancer, but not normal. So, you do not call it cancer, and then you have the group that you call cancer. Well we are calling all abnormal cells in the prostate, prostate cancer, and it is difficult because if you have Gleason 3+3, in our minds we feel as though this is maybe not a truly aggressive form of cancer, but if we call it cancer, that is the problem. So, the question is do we have to go ahead and reassess how we in fact grade prostate cancer and come up with as I mentioned, a higher resolution based perhaps on genetics? So those Gleason 6 prostate cancers may actually fall into something that may be considered atypia? And again if you have nomenclature like that, I think it then becomes easier for everyone, including the physicians to feel comfortable doing active surveillance and so that is a very interesting point because using the word cancer and then saying, let's just do active surveillance, because how many cancers out there do we do active surveillance on, not many, so this is a paradigm shift change that we as physicians and working with the patients we have to better understand.

Dr. Peter Schulam is a Professor of Urology, Chair of the Department of Urology and Chief of the Department of Urology at Yale-New Haven Hospital. If you have questions or would like to add your comments, visit yalecancercenter.org where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.