

Support comes from AstraZeneca, a biopharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it is a conversation about prostate cancer with Dr. Daniel Petrylak. Dr. Petrylak is a Professor of Medical Oncology and Urology at Yale School of Medicine and Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore You work in what we call GU oncology, that is genitourinary, and there are several cancers that it involves.

Petrylak Yes, that includes prostate, bladder, kidney and testicle cancer. So, there are a number of different areas which we investigate.

Gore Gotcha. And I guess of those prostate cancer is probably the most common one?

Petrylak Prostate is the most common, testicular cancer is the least common. Gore I think a lot of us as we age, hear a lot about prostate cancer and we get into the habit of bowing down before our internist once a year and seeing what is going on. So, I think that is what a lot of us are afraid of.

Petrylak I think there is a lot of fear in men over the diagnosis. And it is very, very interesting to see that originally when the advertisements were done for prostate cancer screening, they were done in women's magazines because the wife used to drag the husband into the office to get checked. There has been an evolution of thought on the use of screening in prostate cancer. A couple of years ago, the United States Preventative Task Force came out with a recommendation of D for prostate cancer screening.

Gore What does D mean?

Petrylak D means that they do not recommend it. And now that has changed, they have modified that position, a variety of different groups have also modified that position. There has been a drop in the death rate of prostate cancer. In the 1990s, about 40,000 men were dying from metastatic disease. This is down to about 27,000 men projected for the year 2018.

Gore This is still a lot of people.

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Petrylak It is still a lot of people. It is the second leading cause of cancer death in men. And it is most prominently diagnosed in men as well.

Gore What does screening involve? Blood tests and a rectal exam, right?

Petrylak Blood test, rectal exam and then if the PSA is abnormal with the rectal exam abnormal, that leads to a biopsy to determine if the patient has a malignancy.

Gore How has it changed from suggesting that nobody get it?

Petrylak I think what has happened is, there is recognition that there is now more metastatic disease since that recommendation. The PSA test should engender a discussion between the physician and the patient about what they should do about it. PSA of greater than 4 is considered to be abnormal, and it may not be appropriate for an 87-year-old with congestive heart failure to have a PSA drawn, but a younger man who has 30 years of life ahead of him, may have a family history, that is the patient that we would like to focus on, and of course, we want to catch curable disease early and if the disease is more advanced and comes forth with multi-modality treatment, but I think again it does not substitute for being a good physician and talking to your patient about what needs to be done at a given situation.

Gore Let's say I chose to get screened, which I personally do, and I have been fortunate to have low PSAs, let us say mine was 4 or 5, somewhere in there, which I know to be over the upper limits of normal, now I am feeling kind of worried, what happens next?

Petrylak We refer you to a urologist, the urologist will perform a biopsy, also an ultrasound of the prostate to see if there is tumor present. Gore Even if my rectal exam does not suggest one, is that right?

Petrylak You can have tumor present with a normal rectal exam, that is correct. Gore Okay. And even if the ultrasound or whatever does not show anything right?

Petrylak Correct.

Gore So, I get a biopsy and then what?

Petrylak Then let's say if you have cancer diagnosed, let us take the worst-case scenario, it all depends upon your extent of disease, what the Gleason score is, how extensive the tumor is within the prostate. So, if you have a low-grade lesion, it is a Gleason 6.

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Gore What is Gleason?

Petrylak Gleason is a way of measuring the degree of aggressiveness of a cancer. For example, Gleason 10 is the most aggressive, it is taken from the most common patterns that the pathologist recognizes, a 5 + 5, and that is somebody who has very aggressive disease. A Gleason 6 is prostate cancer that you die with and not from. And so, there are a variety of different iterations on that

particular scale and different risk groups. But the Gleason 6 is the lowest risk and the Gleason 10 is the highest.

Gore There is no 1 through 5?

Petrylak There are, they are not common. But again, the Gleason score, a pattern is 1-5, and then the score is the 2 most common patterns. $3 + 3$ equals 6, $4 + 3$ equals 7, $5 + 5$ equals 10. Gore The $2 + 2$ would equal 4.

Petrylak Right. Those are not common.

Gore Let us say, I was a lucky guy and I had a 6, then what?

Petrylak So, your physician and you should have a discussion about what to do next, and this could include observation or watchful waiting. It also could include radical prostatectomy or radiation therapy. It all depends upon how extensive the tumor is and how extensively involved the gland is, and again what your goals are. If you are a person who may be 85 years old and have congestive heart failure, you may not be able to go forth with a surgical procedure. Also, it may not be appropriate to do a PSA in that type of patient. But again, I think it depends upon a discussion as to what you feel are the important impacts on your quality and quantity of life.

Gore I know that this is a very stressful decision, we had a close relative in my family who went through this in the last year and struggled mightily with this decision and opted for radiation, which is not necessarily the decision I would have made, but really struggled with deciding, again side effects are different with these treatments right?

Petrylak Absolutely. And often patients come to see me for “the unbiased second opinion.”

Gore Because you are not a surgeon and you are not a radiation doctor?

Petrylak And the way I present it to them is we do not have randomized data showing that one treatment is a better cancer treatment than the other.

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Gore They are both about the same as far as we know, right?

Petrylak Right. In fact, if you look retrorespectively, and you match the Gleason score and the clinical stage of each patient, it seems as if the survivals in retrospective studies are the same for radiation therapy and surgery. So, the way I put it to the patient is, given the fact that we really do not know and maybe they are the same as far as an anti-cancer treatment is concerned, what side effects are you willing to put up with and then what treatments if this does not work out as your primary treatment, what treatments could you then go forth with safely afterwards? For example, if a patient has their prostate out and the PSA begins to go up, it should go down to 0 after the surgery. We

often give salvage radiation therapy to the patient in that situation. Side effects are the continence levels are frozen at the level that they start out with or they may also have more sexual dysfunction. The opposite is a little bit more difficult to do. So, if a patient has radiation therapy and then decides I want to go for salvage prostatectomy, there is a higher rate of incontinence. So, I think that you have to look at the overall picture as to what the patient is looking for. Yesterday, I counseled somebody who is young, 50 years old, and he was about to get married and he wants to have children. And also wants to be sexually active. So, that engineered itself into a very, very long prolonged discussion about what to do, sperm banking in that particular situation and how that may affect the couple because remember it is not just the patient who is affected by it, it is the spouse as well.

Gore Can you let us know what the patient decided?

Petrylak We decided to go for surgery. He is leaning towards surgery at this particular point.

Gore So, he will bank his sperm? Wow, I can see that it would be hard because the loss of sexual function is a reality, a real possibility, although I guess that is also a true with radiation, right and not everybody maintains their sexual function, is that right?

Petrylak That is correct. If a patient does not undergo hormone therapy, which we often do with radiation for a high-risk patient, the patterns of sexual dysfunction are different in prostatectomy. So, with prostatectomy, you have a shock to the system and you gain your potency over time. So, if you are going into a surgical procedure potent, you have 50:50 chance of coming out potent at some point depending upon the surgeon, depending upon the extent of disease. If you get radiation therapy, you gradually lose your potency over time. So, at 2 years, it is 50:50, it is about the same, but it is because of fibrosis that develops, scar tissue that develops during the radiation treatment or after the radiation treatment, at least that is theory.

Gore I remember hearing a lecture here at Yale a year or two ago from a urologist that apparently quite a lot is being done with people who have had prostatectomy in terms of trying to preserve sexual function if they refer to such a person or if the urologist knows how to do that right away, right?

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Petrylak There are nerve-sparing procedures, there are nerve grafts that are being done as well. So there are a variety of different ways of trying to maintain the sexual function and also the postoperative period is crucial, giving drugs like Viagra or other drugs that may promote erectile function. That is helpful. And there is a vascular issue that goes on as well. So, the interesting thing is that often the testosterone levels in these patients can be a little bit on the low side when they start off, sometimes they rebound up after the surgery and we do not

really understand why, but that also plays a function as well.

Gore But the good thing for patients who make either of these decisions is that most of them, if it is an early-stage cancer, are likely to be cured, right?

Petrylak About two-thirds of patients after prostatectomy should have their PSAs go down to less than 0.1, the other third is considered to be a biochemical relapse, whether that turns out to be clinically significant is another issue. That is one of the more controversial areas of prostate cancer management.

Gore So, what do you do for these patients whose PSA starts to rise?

Petrylak #1 -- you assess if there is any disease outside the prostate. So, we have some newer tests that are now being developed, such as Choline PET scan, which is a way of trying to detect prostate cancer outside the prostate bed. Standard imaging is also used in the situation, like CAT scans, bone scans and we look at how fast the PSA is going up, the PSA doubling times. A patient who has a PSA doubling time of less than 6 months and relapses within a year of surgery, that is a patient you really want to be concerned about. Because that is somebody who behaves as if they have de novo metastatic disease because their cancer spreads. You've got to be very, very aggressive with that patient. Interestingly, the big dilemma is when do you start hormone therapy, and there are studies now that combining hormone therapy with radiation therapy for biochemical relapses, we are also looking investigational at vaccines in the situation, this would be the perfect situation with low-volume disease before it spreads to look at immune treatment, so there are a variety of different standard treatments as well as investigational treatments that are now being evaluated.

Gore And when you talk about hormone therapy, you are talking about blocking the effects of testosterone right?

Petrylak Exactly.

Gore So that sounds like that might have a few nasty side effects as well.

Petrylak You know, we are realizing more and more that hormone therapy is not just loss of sexual function. There is weight gain, there is loss of muscle mass, there is osteoporosis, fatigue can be an issue as

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well. Men claim, "I feel like the wind is being knocked out of my sails." That is a really common complaint. So, when you have got a 50 or 60-year-old who has 20 or 30 years of life ahead of them in that situation and you are committing them to long-term therapy, that is a very, very big decision, so again, we being doctors, we are looking at our patients as a whole in addition to the cancer in this situation.

Gore This is very fascinating and a very important topic for our patients and our audience to learn about. Right now, we are going to take a short break for

medical minute. Please stay tuned to learn more information about prostate cancer with Dr. Dan Petrylak.

Medical Minute Support comes from AstraZeneca, a biopharmaceutical business with a deep-rooted heritage in oncology and a commitment to developing cancer medicines for patients. Learn more at astrazeneca-us.com. This is a medical minute about lung cancer. More than 85% of lung cancer diagnoses are related to smoking and quitting even after decades of use can significantly reduce your developing lung cancer. For lung cancer patients, clinical trials are currently underway to test innovative new treatments. Advances are being made by utilizing targeted therapies and immunotherapies. The BATTLE-2 trial aims to learn if a drug or combination of drugs based on personal biomarkers can help to control non-small lung cancer. More information is available at YaleCancer-Center.org. You are listening to Connecticut Public Radio. Gore Welcome back to Yale Cancer Answers.

This is Dr. Steven Gore and I am joined tonight by my guest, Dr. Dan Petrylak who is a professor of medical oncology and urology, and we have been talking about prostate cancer. Dan, I am hoping we have some time to talk about bladder cancer as well, but again I think people are very interested in prostate cancer and I know that over the years, people have been very worried about if they have metastatic prostate cancer, there might not be many treatments. Is that still the case?

Petrylak No that is not the case. There has been a tremendous amount of research and new drugs that have been approved by the FDA for metastatic prostate cancer. It has really evolved very, very nicely over the last 15 years. So, in 2004, there were 2 drugs approved for metastatic castration-resistant prostate cancer.

Gore Castration-resistant? What does that mean? I do not want to be castrated.

Petrylak No, in fact, patients absolutely hate that term.

Gore I hate it.

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Petrylak There is a movement now towards changing it to endocrine-resistant, primary endocrine-resistant because as we had written in an editorial a couple of years ago, it is both pejorative and descriptive. We want to take the pejorative part out of that description, but let us take a patient who comes in to see us who has got newly diagnosed metastatic disease. The testosterone levels are normal, let us say they are 400, they have disease in the bone, they have disease sometimes in the lymph nodes, sometimes in the liver as well and that is actually a poor prognostic presentation. So, the first treatment we would go forth with is androgen-deprivation therapy, which would be to deplete the body of testosterone. There are a couple of ways that we can do that. One way is

to short circuit the signal that goes between the brain and the testis that tells the testicles to make testosterone. The second way is blocking the binding of testosterone to its target, like a lock and a key, the testosterone is the key and it goes into the lock and then turns on the cancer cell and makes it divide. So, by depriving the body of testosterone in addition to those symptoms I mentioned before – the side effects, we will cause the cancer cells to regress. It does not cure it, it makes it get better, you can see PSA declining that goes from 1000 to 0. You can see improvements in urination. We have had patients who have had spinal cord compression from cancer that goes to the back and it obstructs the spinal column, that can improve and patients can start walking again. So, there are dramatic improvements in the symptoms and the volume of disease. The trouble is not curative, and after about 18-24 months, the patients then begin to progress. When I first started out in the field in 1989, there was no treatment that improved survival, in fact we wrote several papers at that time saying the chemotherapy did not work, and then we started looking at the taxanes in that situation, such as docetaxel.

Gore These are chemotherapy drugs?

Petrylak Chemotherapeutic drugs, that is correct. We started seeing modest improvements in survival and I was the lead author on one of the trials that got docetaxel approved in 2004 for castrate-resistant prostate cancer. And then there was a gap for a long period of time until about 2010, no new drugs were approved for this disease and then we started seeing the pay off. Immune therapy with drugs such as Provenge which is a way of activating your T-cells outside of the body that shows a survival benefit. Other chemotherapeutic drugs such as cabazitaxel were approved by the FDA, and the interesting thing that was found that even though the levels of testosterone in the body were low in the blood stream, the tumor cells learned how to make their own testosterone. So there are drugs such as abiraterone, otherwise, known as Zytiga or Xtandi which will deplete the testosterone or antagonize the testosterone within the cancer cells and give us secondary improvements and improvements in survival. There are also isotopes that target the bone, radioactive isotopes and not only do they improve pain but they make the patients live longer. And the drug that we think about is a drug called radium-223 discovered by Madam Curie a number of years ago, a long time ago, more than 100 years ago. But these are treatments in our armamentarium and the real challenge is how do we sequence them, how do we decide on one versus the other. So, what we are finding now is moving some of these treatments up at the very beginning when patients first undergo hormone or androgen-deprivation therapy, that gives us

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more bang for our buck. So, we can see survival improvements of 18 months to 20 months rather than 3 or 4 months. And so, our trends now are to move these drugs up earlier in the course of the disease. The other thing that we are trying to develop and we are actively involved in this at Yale is personalized medicine

or the personalized approach to patients with resistant prostate cancer. About 1 in 3 patients will have a deficiency in the ability to repair their DNA, and I am sure you have talked on the show about BRCA and the breast-related genes that are transmitted to patients. There are also other enzymes that are involved in DNA repair. Well, about a third of patients have that deficiency in prostate cancer, and this has been recognized very, very recently. So, there are drugs now that we are trying to design based upon the signatures and phenotypes that we see from the tissue and rather than giving a patient a drug that may be ineffective and toxic, we are now beginning to focus on giving the right drug for the right patient. So, the field has evolved significantly over the past 20 years or so and I cannot wait to see what is going to happen over the next 20 years. Gore That is great, but it still sounds like if we can prevent the development of cancer spreading outside of the prostate, that is really the best thing for the patient right? Petrylak Absolutely. And once it becomes metastatic, at this time, it is incurable.

Gore So even though you are making what sounds like really terrific advances, this is something that men of a certain age, maybe you should tell what the age is, but men of a certain age should at least be talking about the pluses and minuses of screening with their internists.

Petrylak Yeah. It depends upon which society you listen to.

Gore Well, I want Dan Petrylak's opinion.

Petrylak My opinion is, you should start screening at the age of 50. If you have a family history, also if you are African-American, you should be looked at earlier, age 45. And the incidence of prostate cancer in African-Americans is higher than the general population. The question is, is the disease different, and we really do not have good answers to that at this time because we do not have enough data and we need more encouragement into the entry into clinical trials for patients of different ethnic backgrounds so we can understand this better.

Gore Got it. So, at what age should African American men be screened?

Petrylak I would say 45.

Gore And obviously if there is family history for them, perhaps even younger than that?

Petrylak Perhaps even younger, yeah.

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Gore I do not want to have you on the show and not talk about your interest in bladder cancer, which is something that I know you are very passionate about. What is going on with that?

Petrylak There have been a lot of great things going on in bladder cancer. This

is a field that was really not moving at all when I first arrived here in 2012. And if you had metastatic disease, your survival was about 15 months. There were proportionate patients, 5%, who had long-term survivals with chemotherapy, but really nothing worked well. And then, we pioneered, we were one of the pioneers in checkpoint inhibition therapy for bladder cancer.

Gore This is some kind of immune treatment?

Petrylak Immune treatments, exactly. So, the trials we just published are long-term data with atezolizumab, which is a PD1 inhibitor that is one of the ways of the immune system causing as we call the Darth Vader effect where it masks itself from the surveillance of the immune system.

Gore You mean, the tumor if I am understanding you, puts on like a cloak of invisibility from the immune cells?

Petrylak Right, it is a cloaking device.

Gore Gotcha, and then you have a medication that takes away the cloak?

Petrylak Exactly. And this works dramatically well in about 1 in 4 patients, and we have shown the survival is better with these drugs and clearly it is a big advancement and move forward, but again 1 in 4 patients will have a good response, so we are looking for other ways of improving on that. And there are two different approaches we have taken. One is to go back to standard chemotherapy and we just published some data that came out recently and presented in the ESMO meetings back in the fall of a drug called ramucirumab, which is a drug that inhibits some of the chemicals that cause new blood vessel formation. And bladder cancer is very vascular, it has got a lot of blood vessels. And when we combine this with a chemotherapeutic drug called docetaxel, we found that the tumor shrinkage rate was double with the combination compared to the single agent, and we also found that it delayed the cancer progressing. We are still waiting for the survival data and we hope to have that within the next month or two, but we are very excited about that. The other thing that we are excited about is what we call targeted immune therapy agents. These are drugs that use a monoclonal antibody which is like a dart, that you are throwing at a dart board, it is a specific way of hitting the cancer cell, and there is a chemical called nectin, which we know is expressed in about 90% of bladder cancer. So, we have got nectin, we have linked it to a chemotherapeutic agent, it goes directly to the cancer cell, gets internalized, the cancer drug is chopped off and then causes its anti-tumor effect. We found about half of patients who have either failed immune therapy or who have responded and then progressed on immune therapy, are responding to this, so we are very excited about the trials that we have opened now with this drug,

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it is called enfortumab vedotin. It is a very, very promising treatment and so we have gone in an area where 5 years ago there was absolutely no activity. One of

the things we are worried about is we have more clinical trial slots than patients to fill these clinical trials.

Gore Well, that is a good problem you have.

Petrylak It is a good problem I have.

Gore I am sure by the time it gets FDA approved, you will have some cute name like bladder squasher or something like that. And just like the men worried with prostate cancer, about sexual function, I think people with bladder cancer are really worried about continence or how they are going to urinate.

Petrylak Exactly. If they have their bladder out, there are ways of overcoming issues with continence, there are what we call continence diversions, where sometimes patients can urinate normally through their organs.

Gore Through their regular urethra?

Petrylak Well, it depends upon how extensive their tumor is. Because the urethra sometimes is involved as well actually. There was a case reported in the New England Journal of Medicine about Hubert Humphrey, the vice president, who actually had his urethra involved and refused to have a urethrectomy at the time of surgery. So, he wound up dying from metastatic bladder cancer. But if the urethra is not involved, the urologist can potentially construct a new bladder out of the intestine and then when it is hooked up to the urethra, the patient is able to urinate regularly through the penis like they would normally. And there are also similar types of common diversions for women as well. So, this is an extremely important effect on the patient's quality of life, they do not necessarily have to wear a bag, but it all depends upon what their extent of disease is and that really needs to be discussed with the surgeon who is taking care of them.

Gore And these people with these continent diversions where they are using a urethra, are they able to void spontaneously or do they have to catheterize themselves?

Petrylak Well, it depends on the patient. Sometimes they can and sometimes they cannot.

Gore It is amazing what people can do, right?

Petrylak Yeah absolutely.

Gore But the bottom-line is that it is most important to be screened when appropriate, so what would patients, how do patients with bladder cancer come to your attention?

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Petrylak Usually it is nonspecific hematuria.

Gore Blood in the urine?

Petrylak Blood in the urine. The one thing that often patients are shocked at is when I say bladder cancer can be caused by smoking, and they are shocked because they do not associate smoking with the bladder.

Gore I do not smoke with my penis.

Petrylak No you don't.

Gore I don't smoke at all by the way.

Petrylak But the point is that the carcinogens that occur from bladder cancer sit in the bladder and if your urine is sitting in the bladder itself and then you urinate, but it is the chemicals that you inhale. Interestingly, in Connecticut, compared to the rest of the United States, Connecticut has a higher rate of bladder cancer than the rest of the country.

Gore Do you know why that is?

Petrylak We do not know at this point. It is the fourth leading cause of cancer in Connecticut, fifth leading cause of cancer across the United States. So, whether that is related to smoking, whether that is related to other chemical exposures that we may have, certainly that is something that we need to investigate and try to understand.

Dr. Daniel Petrylak is a Professor of Medical Oncology and Urology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.