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Welcome to Yale Cancer Answers with doctors Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week Dr. Higgins welcomes Dr. Nathaniel Lester-Coll for a conversation about prostate cancer. Dr. Lester-Coll is a Resident in the Department of Therapeutic Radiology at Yale School of Medicine and Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences.

Higgins I thought maybe we could discuss some of the general concepts centering around how we treat prostate cancer and how prostate cancer is a multidisciplinary approach of surgery, radiation, and also including hormonal therapies.

Lester-Coll For localized prostate cancer, prostate cancer that has not spread anywhere, we think about ways of treating the prostate gland itself and essentially there are 2 fundamental ways you can do that. You mentioned surgery, and urologists are typically involved and a surgery called radical prostatectomy is a way of essentially removing the prostate and an alternative to that is to treat the prostate with radiation therapy and as a radiation-oncologist that is essentially what I do and that is a noninvasive and alternate way of treating prostate cancer. We tend to think about prostate cancer in different groups, so we think about low, intermediate, and high risk disease and that is based on a blood test called a PSA and also what the cells look like under the microscope, so the more aggressive looking we tend to think of those as more higher risk cancers and higher risk cancers tend to derive a benefit from hormonal therapy as well and that is typically combined with radiation therapy in the treatment of intermediate and higher risk prostate cancer.

Higgins I think it is important for us to just touch on the fact that there is sort of a continuing of risk, prostate cancer is a variety of different diseases of different levels of aggressiveness. You said, we look at the PSA, which is a blood test, so that is one thing that is very concrete, but then there is the Gleason grade, which people hear about, how do we determine a Gleason grade by looking at the cells under the microscope?

Lester-Coll Essentially this involves a different group of doctors called pathologists, and basically their job is to look at these tumors under the microscope and what they are looking at is how closely do these tumor cells resemble the natural normal cells in the prostate and the less that they resemble the normal cells and the more distorted they are, they will get assigned to a higher Gleason grade, and are also considered to be the higher-grade cancers.

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Higgins We are going to talk about this with relationship to your research but the grouping of low, intermediate, and high risk really helps us to figure out just how aggressive our treatments need to be and how we are going to approach those patients, because one thing we know is that there are men who live with the low level, nonaggressive prostate cancers for their whole life and may never see a consequence of that and then, there are the higher risk patients who will probably in their lifetime have a consequence from it and I think that is a big part of your discretion as well as the urologist. Could you go through that for us? You have to educate the patient about something that is really actually very complex.

Lester-Coll Yes, it is very complex and it is very individualized and catered toward the individual patient. One thing we haven't talked about is not treating prostate cancer is also considered a good option, particularly for men with low-risk disease, where we think there is actually a very low chance that the prostate cancer will go outside the prostate and spread and cause symptoms and so not treating it or doing what is called active surveillance is actually now becoming standard of care in the US for men with low-risk disease and we have a lot of good data to support that is a very safe option. In conjunction with their urologist, essentially what that entails is getting a blood test, usually twice a year and getting a biopsy once a year and as long as it stays low risk, there is no reason to do anything about it, you can just continue surveying it and then if at some point, they say, now we found some higher grade disease, maybe that is when it is time to think about one of the treatment options like surgery or radiation.

Higgins I think that is an important point to make, just because you get a diagnosis, there are sort of calculated risks and we have tools now that are actually very reassuring that help people when they have to make the difficult decision of, oh I have cancer, but I am not going to really treat it right now and that is a tough discussion to have.

Lester-Coll It is and I think again, we are moving towards individualized decision making and trying to take into account the patient's own goals of care. There are some people who have that issue where they say, I know I have this cancer and it keeps me up at night, I really want to get this treated, and if that is consistent with the patient's goals of care, then I think it is reasonable to do that, even potentially for lower risk disease. I really try to think about the patient's own preferences and then of course what the side effects are from the treatment because the treatments, whether it is surgery or radiation with or without hormone therapy there are side effects.

Higgins I thought maybe we could talk about some of those things. I have had some surgeons as guests who talked about the risks of surgery, but maybe we could talk about the things that can come after surgery like radiation therapy and hormonal therapy.

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Lester-Coll I think it used to be very difficult to think about side effects comparing 1 treatment to another, but we actually have a study that came out this past year, the ProtecT study, which took men with prostate cancer and they were randomized to different groups of surveillance, radiation, and surgery and I think for the very first time, we have a really good idea of what the different side effects are in comparison to one another. The study essentially showed that there was no difference in outcomes, so a lot out of this really comes down to what those side effects are and so it turns out that, the men who underwent surgery had more difficulty with erections, sexual dysfunction, that was statistically higher in the men who underwent surgery and the men who underwent radiation therapy had more difficulty with gastrointestinal problems, like loose stools and that sort of thing and so I think that data really can help guide us in terms of if one of those side effects is particularly important to someone, I could not stand living with one of those, then it can help us pick which treatment is right for them. Higgins And fortunately, we have a lot of effective therapies and now we can really have conversations, as you said very well informed discussions with patients, about what the incidence would be of potential side effects if they received, let's say, surgery versus radiation versus hormones. Let's say you are radiation-oncologist, the patient comes in to your office for a consultation and after a discussion, that person is going to have radiation therapy as their primary treatment. What kind of things do you discuss in terms of treatment and what kind of side effects they can expect short term and long-term?

Lester-Coll The standard way of treating prostate cancer with radiation therapy is called external beam radiation therapy, so it is a noninvasive treatment, it essentially involves the patient lying flat on a table and a big machine that rotates around the patient and delivers the radiation to the prostate and it is kind of like getting an x-ray, you do not feel anything, you go home that same day, and it is not to say that it is not without side effects. There are some side effects that the patients can experience with time and so those would include potentially some fatigue, they may just find that they are more tired at the end of the day. Sometimes the prostate gland can get a little inflamed and cause some bladder irritation, so maybe having to urinate more frequently than they did prior and potentially some loose stools as well and those side effects are usually temporary if they happen at all, some men do not experience them, but they are typically temporary. The risk of having permanent problems with bladder function or stools is pretty low based on those studies, like a couple of percent, and we have ways now of even trying to lower the likelihood of that happening, working with your urologist, we are using a technique where we actually inject something between the prostate and rectum called

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SpaceOAR and we think that that actually would lower the dose to the rectum and we actually have data now that suggests that it lowers some of those GI

side effects that we talked about.

Higgins Because one of the things we face with prostate cancer is that it is an organ sitting near other essential organs and in the front, you have the bladder, in back you have the rectum, and then underneath the prostate, we have the nerves that control erection and sexual function. These are sort of the challenges for us as a local therapy. Now, you are talking about external beam radiation therapy, the type that we give a little bit each day over many weeks, 6-7 weeks, but some people hear radiation therapy and they think about implants and they say, my uncle got the implant, how was that different than the type that you are talking about?

Lester-Coll Again, the kind I am talking about, we typically do 44 treatments, Monday through Friday, so a very lengthy course and an alternative to that, as you mentioned, are radioactive implants and that is a little bit more like a surgery, although not quite as involved, and that actually involves putting in seeds directly into the prostate gland and that is done once, usually under anesthesia and that is an option too for certain men with low to intermediate risk disease, they need to have a small enough prostate gland, so that is one criterion that we use and that can just be determined by a simple ultrasound study and then where I think the field is potentially going in terms of external beam is we are trying to figure out if we can shorten it, similar to what has been done in the treatment of breast cancer, so that is something that is being studied as well.

Higgins Just to go back to the external beam issue and how that is done, you said 44 treatments, come in and get a little bit of radiation every day and that is like an x-ray type of treatment. As you said the prostate implant is more of a surgery and the little radiation seeds are placed right in the prostate and then that really works by having those seeds in place permanently.

Lester-Coll That is right, they do not come out, they are implanted permanently.

Higgins And then over time, the seeds will give off the requisite dose to take care of their prostate cancer. With regard to the hormonal therapy, that is another area we are focusing a little bit here on quality of life issues and we have some long-term side effects from radiation, but one of the things that we often hear patients talk about are the side effects of hormonal therapies, I thought we might start with why would you even use a hormonal therapy and what types do we use?

Lester-Coll This is best in men with high-risk disease. In men with high-risk disease, we have lots of really good data to suggest that when we add hormone therapy to radiation outcomes

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are much better in terms of the likelihood of curing the cancer, men live longer when they get it and so the standard kind of hormone therapy that we typically

use is something that actually blocks the pituitary gland and that is the hormone that we have up in the brain that secretes a lot of the hormones in our body and basically, we prevent that gland from telling the testes to produce testosterone, so effectively what we are doing is lowering the amount of testosterone that is being produced by the testes and a very common drug that is used to do that is called Lupron. It is an injection that is usually given every 3 months or 6 months and again, what we are doing is we are decreasing the amount of testosterone in the body and testosterone, we think is kind of the fuel that the prostate cancer cells use to grow and so we take that away, combining that was radiation and our outcomes are improved.

Higgins That is a great overview of the 3 different ways that we attack this disease, surgery, radiation, and then talking about the prostate as a hormonally sensitive organ. What we are going to do is, we are going to talk about your research in the next half, but right now, we are going to take a short break for a medical minute, please stay tuned to learn more about the treatment of prostate cancer and risks and benefits of hormonal and radiation therapy with Dr. Lester-Coll in the next half of our program.

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Higgins We talked about the treatment of prostate cancer in the first half covering the general concepts around surgery, radiation therapy, and hormonal therapy and I thought that in the second half, we would discuss some of the survivorship issues including quality of life and one of the treatments that often comes up when we discuss quality of life and long-term side effects is hormonal therapy. Can you tell us how hormonal therapy affects men?

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Lester-Coll As we talked about earlier, hormonal therapy works by lowering the amount of testosterone in men and that is not without its side effects. Most men will experience a lot of general fatigue and sort of malaise after, loss of sexual libido is a very commonly encountered problem and actually hot flashes,

and men will experience hot flashes too, it is pretty commonly seen and there are some potential sort of long-term effects that can happen too. Problems with bone density, men can have accelerated osteoporosis and there is a controversial area about whether men who receive hormonal therapy are at higher risk of developing heart disease and dying from heart disease.

Higgins That is an important thing because as Americans 2 big issues are cardiac and cancer right now and what is the theory behind that?

Lester-Coll It was first observed in some very large analysis that were done in the United States and also in Sweden and some randomized trials where they went back and they said, what happened to the men who got the hormonal therapy, were they at higher risk of dying from heart attacks and really the data is kind of mixed at the end of the day, but the thought is that it may lead to changes in sort of good and bad cholesterol and may lead to an adverse cholesterol profile and also can cause what is called metabolic syndrome, so changes in the body and changes in fat deposition that we think of as being actual risk factors for heart disease.

Higgins This is interesting because survivorship centers around all of these things and the fact that, we sort of leave an imprint on the patients, although we cure a lot of patients, they have to live with these long-term side effects and I think that we are now able to really step back and say well, now that we have even more survivors, we really need to pay more attention to not just how long they are going to live, but how will they are going live. This is an area where you have done some research, which is, how do we measure not just not quantity of life but quality of life?

Lester-Coll Measuring quality of life and patient reported outcomes is becoming increasingly a part of clinical trials now, so we are looking at how patients feel and what symptoms they are reporting and also what doctors think in terms of scoring the symptoms, but you mentioned what is the way to quantify it. Traditionally, we have just looked at survival in most studies, but there is actually a way of trying to quantify quality of life and that is what is called quality adjusted life expectancy or quality adjusted life years or QALYs and so QALY is this idea that a year spent living with prostate cancer or having side effects from treatment is probably not worth the same as a year spent in perfect health. So we might say, based on trying to elicit the score from men that may be under treatment and having those side effects is worth, I do not know 80% of the year spent in perfect health and so we can look at that as a quantity and adjust our outcomes based on how much

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time patients spend either being under treatment or living with side effects or having some of those permanent imprinted side effects like you mentioned.

Higgins And this goes back to our discussions that we have with the patients

that the prostate cancer treatments are complex, but then the long-term survival and long-term QALYs or quality of issues are also important and now, I think starting a conversation where we can be as informed about that as we are about some of the other more concrete things that we used to, things like PSA, we looked at Gleason, we looked at how many months of survival you might gain from a different treatment, but it is again not just how long you live but it is how well you live, so I feel very encouraged about the fact that we are able to give patients something that is so valuable, which we were unable to before.

Lester-Coll My hope is that this kind of research will facilitate that individualized, patient-centered decision making and maybe for a certain individual being alive, but having some of the side effects from the cancer or the treatment, that really may take a toll on someone and they may say, I really could not live with this side effect or that side effect and that can really help patients come to a decision about what is right for them.

Higgins I think that is so important and I wanted to just get into the specific issues that you discussed in your paper that recently came out in the JNCI about hormonal therapy in intermediate risk prostate cancer and this is an interesting group because there is a lot of controversy as to how to treat them.

Lester-Coll Right, we have all this great data in high-risk disease, we know adding hormonal therapy to radiation really improves outcomes, but what about men with an intermediate-risk disease, where that benefit may not be as robust? There was a big European trial that was published this past year that looked at this question, and it took men with intermediate risk disease and treated them with radiation with or without hormones and they saw differences in terms of the likelihood of their PSA scores being good. That is, their PSA scores were not rising, but there were really no differences in survival in that study and so we wanted to take that data and create a model where we could look at not just the cancer outcomes and survival, but also what about the side effects from these different treatments and potentially test this interaction with hormonal therapy and cardiovascular outcomes and so we did that by using some data from the Framingham Studies. The Framingham Studies were big heart disease studies that took families who live in Framingham, Massachusetts and they studied them for decades and that is how we determine that things like blood pressure and cholesterol, smoking, diabetes, that these are risk factors for heart disease and so in our study, we were able to stratify patients and break it down by whether they had 1, 2, 3, 4 of those risk factors or if they had a history of a heart attack and ultimately, what we found in these men with an

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intermediate-risk disease is that we could not see much of a benefit for adding hormones if they had a previous history of a heart attack and we think that the life expectancy is probably different in that patient population and so again with intermediate-risk disease prostate cancer, it suggests that they should probably

be focusing on the heart disease and that is probably more of an important issue for them than aggressively treating the prostate cancer.

Higgins I think this also plays into the survivorship issue, just like in breast cancer. I think we have so many prostate cancer survivors, that being well informed about not only when they walk into the clinic and we do this type of counseling, but being informed about lifestyle issues and how they affect, #1 your potential outcome and weighing your potential benefits and risks of particular type of treatment like hormonal therapy, but also in follow up, we have the patient see a survivorship counselor and lifestyle issues come up there too.

Lester-Coll Right and actually, one thing that we found in our study was that it really did not seem like the benefits of adding the hormonal therapy were seen until a very, very long time, really 10-15 years out. You are talking about having all of these side effects from treatment in the short-term, not feeling well, decreased libido, all these things and really for a gain that may not manifest for a very long time. I think that is a really important concept and an important finding of our study is that someone who is thinking about where they are now and where they may be 10 years from now that may be in a very different place and you have to help people think about the long-term outcomes.

Higgins Which is sometimes difficult because I think I have treated prostate cancer patients in the past and of course, when you see them in consultation, the first thing on their mind is usually I have cancer, I have to get treated and there is a lot of urgency, there is a lot of fear around that, so a lot of people feel very reactive and want to just proceed, but there has to be a sort of stop and reevaluate point when you are doing the counseling, where you think okay this is #1 for most people not an emergency, we have to think very long-term, not just about next month or next year, but maybe 10 years ahead.

Lester-Coll Right and so that is why I am sure you experience that these consultations take sometimes 1-2 hours right, because we are really spending a lot of time thinking about these issues and weighing these very difficult decisions about should someone get treatment and what are the side effects short term and what are these outcomes going to be later down the road? Our hope is that these kind of studies will at least provide patients with more information so that they can make educated decisions with their doctor about what is right for them.

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Higgins We live in a society where people are living a very long time and we are able to now have different tools from internal medicine from other studies from similar longitudinal studies like the Women's health study, the Framingham study, where we can really predict now with better certainty what do we expect in terms of this person's future health, future longevity and then put



that together with the cancer diagnosis in a more sophisticated way than we really could in the past.

Lester-Coll I think before we were more fixated on the cancer itself and now we are trying to think about the bigger picture, these are the comorbidities and what else is going on and of course, as we talked about earlier in show, what are the patient's preferences in terms of their own goals and their own goals of care?

Higgins So highly personalized.

Lester-Coll Right.

Higgins One of the things that came up as I was thinking about this is that the randomized trials that we are doing on many diseases now include some of these quality of life indicators and that was not the case in the past, maybe you could discuss that a little bit?

Lester-Coll Again, there are different ways of measuring quality of life and I think the simple way to think about it is what does the patient feel and what is the doctor observing and so that is very important because oftentimes we find that those scores can be very different, patients may think that they are feeling much worse than the doctor may be able to detect and that may just be because we have these short fleeting interactions and we do not have that much time perhaps to really get into these details, but what we are seeing, particularly in prostate cancer, is more and more studies are now reporting both patient reported outcomes as well as the doctor's own assessment of what is going on and so I think that is really interesting and adds a lot of really valuable information, especially when again we are trying to make these decisions about which treatment is right for the individual patient.

Higgins Because in the past, in many cases, we are really relying on what the doctor reported, so it was a filtered answer when you asked about a person's quality of life, it was usually filtered through the physician and I think this is just part of a bigger picture of personalized medicine which is really listening to the patient.

Lester-Coll Absolutely.

Higgins Really hearing what they are saying and then also, we have become more sophisticated about this, taking those symptoms and grading them and trying to really put that

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together in terms of a big picture scenario, in other words, how well is this person living and is it something that they are satisfied with? Lester-Coll I think it is helpful to have these kinds of data available to us and in consultation, I try to bring up the studies in assurance, if you get this treatment, here is what patients reported, here is how they felt, here is what they thought, here is what

went well and what did not go well and again, I think that is really valuable information.

Dr. Nathaniel Lester-Coll is a Resident in the Department of Therapeutic Radiology at Yale School of Medicine. If you have questions, the address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu) and past editions of the program available in audio and written form at [YaleCancerCenter.org](http://YaleCancerCenter.org). I am Bruce Barber reminding you to tune in each week to learn more about the fight against the cancer, here on WNPR, Connecticut's Public Media Source for news and ideas.