Episode 12: Prostate Cancer- From Screening to Treatment

Kendal Williams, MD (Host): Welcome everyone to the Penn Primary Care Podcast. I'm your host, Dr. Kendal Williams. So, in our podcast thus far, we've had an opportunity to address a lot of cardiovascular issues with hypertension, cholesterol, and so forth, but we've really never addressed or have not yet addressed the other major domain that we deal with, particularly when it comes to preventative care in primary care, and that is cancer. So, today we decided to talk about one of the most common cancers and that's prostate cancer. With me to discuss that are two experts. Dr. Phillip Pierorazio is a Urologist and Chief of the Section of Urology at Penn Presbyterian.

His expertise is in urologic cancer, specifically. Phil did medical school at Columbia and residency at Johns Hopkins before coming to Penn last year. Phil welcome.

Phillip Pierorazio, MD (Guest): Thanks so much for having me.

Host: Dr. Vivek Narayan is an Oncologist at Penn. He's an Assistant Professor of Medicine. He did residency and fellowship at Penn, and now specializes in urogenital malignancies.

Vivek, thanks so much.

Vivek Narayan, MD, MS (Guest): Thanks so much. Glad to be here.

Host: So let me set the stage and talk about prostate cancer generally. We know that it's a very common cancer, that it remains the second leading cause of cancer death in men. And there are over 34,000 deaths a year from prostate cancer. So it's still, there's still a significant burden of disease out there. We do know also that it affects different ethnicities in variable ways. And it has a clear heritable component. So, it does run in families. There's a two and a half fold, increased risk in those who have one relative with prostate cancer and a five fold increase in those with two relatives.

African-American males are particularly susceptible and present with more aggressive cancers. And, you know, the major challenge, I think of prostate cancer stems from the fact that it actually is very common. And we've all probably heard that statistic, which is accurate that over 70% of men in their eighth decade have some focus of prostate cancer on autopsy studies.

So, this is a very common cancer. There is the risk of over-diagnosis, particularly for older men who will die with prostate cancer rather than of prostate cancer. And that's a lot of the sort of the thorniness that surrounds screening for prostate cancer. So, we're going to start this discussion with screening.

And, you know, now it's primarily PSA measurements that we do. I actually want to step back though and talk about digital rectal examination because you know, when I was in training in the late nineties, we still did digital rectal exams to detect prostate cancer. I, myself, as a resident, detected it on one of my patients and had a successful outcome. So it was something that we did. And Phil, my understanding is that many prostate cancers can be detected on digital rectal exam.

Dr. Pierorazio: Yeah, it's a, great point and a great question. And I will tell you, it is still a controversy in urology now is how many digital rectal exams we need to do. And how important are they? And the short answer is we still do rectal exams on a regular basis. I think it's less and less common in an era where we have kind of saturated PSA screening, that's the sole reason we're detecting prostate cancers by rectal exam alone, but it still is part of the initial screening process.

And when we find an elevated PSA or we find somebody who eventually ends up being diagnosed with prostate cancer, it's certainly part of our clinical staging. So it's an important part of that first visit with a urologist.

Host: So, we're going to talk about PSA's now, but I guess there is the assumption that if somebody has digital rectal exam that suggests prostate cancer, and you know, we're talking about a hard nodular lesion on the surface of the prostate, that their PSA will be elevated, but that's not always true is it? At least not to the degree where we would regard it as positive, right.

Dr. Pierorazio: Yeah, that's absolutely true. The real trick with the digital rectal exam is you'll feel lumps and bumps on men's prostate. And it's particularly because BPH or benign growth will grow in adenomas. You'll feel these lumps and bumps, but it's really tricky to distinguish once I'll, oh, it's a benign lump and bump from something that feels cancerous, which as you said, is often really firm can be fixed. Can often have desmoplasia kind of inflammation around it, that it just has a subtle quality that's different. That's really hard to describe, but yes, it certainly can give additional information from that PSA.

Host: So let's talk about PSA's. This is the universal screening tool, it's obviously been controversial. Phil I just want to get your just general insights about PSA screening. There's historically been debate between internist and urologist and the guidelines sort of reflected the different priorities. But they seem to be merging more in their guidance, but I just want your thoughts on general PSA screening, population-wide like we do in primary care.

Dr. Pierorazio: Yeah. You know, I drank the Kool-Aid. I firmly believed in PSA screening. I think the data is unequivocal that it saves lives when used properly for prostate cancer screening. In my opinion, the real controversy with PSA screening was not for the detection of prostate cancer, but had to do with the over-treatment of prostate cancers and really taking many men to the operating room or subjecting them to treatments that they didn't need for now what we know for men with low risk and very low risk prostate cancer that will get.

Host: We'll get to the treatments later, but it sounds like that's translated into watchful waiting strategies downstream that prevent that overtreatment right?

Dr. Pierorazio: Yeah, and I think that's the number one thing we've realized, you know, urologists got a bad name. Every man with prostate cancer, 10-20 years ago had some form of treatment. And we created a lot of erectile dysfunction. We created a lot of voiding issues and we created a lot of mistrust in the urologic community. And I think now by being more intelligent, by the way, we manage prostate cancer, by really using active surveillance. And we can talk about those terms later why we really prefer active surveillance to watchful waiting and what that subtle difference is. But by employing active surveillance in a much larger population of men with prostate cancer, I think we're gaining that trust back. I think we're doing a better job of screening and treating our patients with prostate cancer.

Kendal Williams, MD (Host): Vivek, I have a question for you. There's a shift in earlier cancer presentations for colon cancer. I know for some other cancers as well, are we seeing that same thing with prostate cancer?

Dr. Narayan: I mean, there's no doubt that with the advent of PSA screening, there was a huge shift in the earlier detection of prostate cancer. So, you know, we saw the huge spike in the incidence of prostate cancer with the coming of PSA screening. I think as sort of Phil alluded to with more intelligent or smarter PSA screening in the more recent years, that actual incidence of prostate cancer is coming down, but we still largely detect prostate cancer at an early stage.

In the Western world, like the United States, only about 5% of men who present with prostate cancer, unfortunately present with a more metastatic or distant metastatic involvement of the disease. So largely we are still detecting clinically localized prostate cancer.

Host: So the guidelines typically start at age 55 in their recommendations, but there is a subgroup of patients who should be considered for earlier screening, even as early as age 40, particularly those that have two relatives or even one relative, or, African American men in particular. Do you guys have any thoughts on that? A screening before 55?

Dr. Pierorazio: Yeah, I do. You know, I have strong conversation with my patients when they come in with, or without a PSA test. And the conversation starts always about what's average risk and average risk is really somebody who doesn't have a family history of prostate cancer. They don't really have any knowledge or symptoms about it. And we start them at average risk. The men who are at high risk, who certainly should start earlier, I put them three categories. Men who have a family history of prostate cancer, as you said, and it could be one or two first degree relatives that have prostate cancer, particularly if that cancer's at a younger age, the second is especially in this country, African-American men. We know these men are at higher risk of developing cancer and developing aggressive cancer at a young age. And the third category I put there is anybody who has had a relative who died of prostate cancer. Prostate cancer deaths are pretty much, I wouldn't say pretty much avoidable, but they are often avoidable with early detection and with contemporary treatments.

And if you've had a family member who died of prostate cancer, particularly at a young age, those people I think are at higher risk for having an early prostate cancer.

Host: So the 55 to 69, both the USPSTF and the American Urological Association, my understanding is they recommend sort of a patient centered approach, discussing the risks and benefits of prostate cancer screening. I have my own sort of elevator pitch that I give on that discussion. I'm curious, what Phil, what do you do, what do you say to patients when you're trying to talk about prostate cancer screening?

Dr. Pierorazio: Yeah, the way I always put is listen to any test or any treatment is going to have risks and benefits, the benefit of screening for prostate cancer is that we could catch a prostate cancer, the downside of screening for prostate

cancers that we could put you through a whole workup that either finds benign disease or diagnoses you with a cancer that doesn't need to be treated.

And if you're willing to undergo all those treatments and potential subsequent diagnostic steps for finding a prostate cancer, then we certainly should pursue screening. And if they're not ready for that, then we kick it down the road or we come back and we have the discussion at a later time and that's my elevator pitch. I would love to hear how you talk about this.

Host: I think that I capture a lot of the same elements that I tell them, listen, you know, prostate cancer is very common. I describe it, that it can be in many cases, a weak cancer, that people will die. I don't know if you would frame it that way with, rather than of and that at certain age groups we could stop screening. I generally do recommend to my patients. They ask me my opinion and I say more knowledge is generally a good thing. And as long as I'm comfortable with my urologists that I work with that they're not going to take them down a path, and that the patient is comfortable understanding that, even if you have prostate cancer, you're not going to necessarily need aggressive treatment at this stage. If they're comfortable with that, then we move forward.

Dr. Pierorazio: Yeah, I think that's a hugely important point and I do stress the same thing. And thank you for bringing it up is that not all prostate cancers need to be treated. And you need to understand that if we're going to screen you and we're going to test you, and if we find a prostate cancer, that doesn't necessarily mean you need aggressive treatment. That's a great point.

Host: So let's talk about PSA. Let's talk about the protein, right? So, when we're doing screening, we're getting total bound, PSA and free, right? No, we're just getting bound PSA, right?

Dr. Pierorazio: You're just getting bound PSA. You have to request a free PSA.

Host: Exactly. So, in our environment, in primary care, we're just ordering that, but you use free PSA to some degree. Right. And how do you use it?

Dr. Pierorazio: Yeah, we will occasionally. And it's really where you see that patient in the borderline realm, in my opinion, where their PSA's in that 3, 4, 5 range. But you know, they have BPH, from their kind of clinical presentation, from their rectal examination. And so you're trying to figure out, is that PSA related to big benign prostate or is there an underlying cancer and that's where

the free PSA comes in. The easiest way to remember it is the higher the free PSA, the higher the likelihood that they have benign prostate.

Host: The higher, the likelihood they have a benign prostatic hypertrophy. If, the free PSA is higher.

Dr. Pierorazio: Exactly the higher likelihood they'd be BPH or the higher that they're free of cancer. Sorry, I'm getting my words tumbled up, and now, there's even newer versions of that. It's still a free PSA and there's some other isoforms, but there's a test called a 4k or something called a prostate health index, which are available at some labs that not only will spit out your PSA and your free PSA, but they'll give you kind of a calculation at the end of that laboratory test that helps put a patient in a category. You've got a 10% risk of having cancer. You've got a 30% risk, you've got a 50% risk, and that really helps us in those men we're not sure if they need additional workup or a biopsy.

Host: Because, you know, we commonly use four as the cutoff, but it's not a black white thing. Right. I mean, it's a spectrum. So there are patients with PSA's in the two, three range who have prostate cancer, right?

Dr. Pierorazio: Absolutely. I just had that conversation with somebody today. Their wife asked what's a normal PSA, and I said, there is no normal PSA. The only way you don't make PSA is if you don't have a prostate. And there's a very wide spectrum and huge crossover between men who have benign prostatic growth and men who have normal prostates and those who have prostate cancer.

Host: When I was in previewing and preparing for this podcast, I read the chapter on prostate cancer in Harrison's textbook of internal medicine. And they made the point that patients who have very low PSA's, less than one don't necessarily need to be screened as often that potentially you could even screen little as every five years. I don't know if that's a practice you do.

Dr. Pierorazio: Yeah. In my practice, I am fortunate since I see a lot of patients with cancer, so that we've kind of crossed that hurdle already, but it is one of the very common conversations in the general urology practices and with my partners. And I think one of the really nice things of this PSA screening controversy has been urologists have also backed off from the frequency of screening.

And so it is much more reasonable and considered reasonable to screen every other year, every third year, every fifth year, depending what somebody's PSA level is, what their risk of developing cancer is based on those categorizations

we've talked about before, and then what's the likelihood that they're going to accept and need an intervention, right? So older man, lower PSA, those things kind of factor into less frequent PSA screening.

Host: Does the change in PSA affect your judgment as well as to when you repeat it? Like, if it goes from one to two, for instance.

Dr. Pierorazio: Yeah. You know, we'll see PSA fluctuations and that's really common. And one of the biggest sources of angst in patients, why, you know, my PSA last time was five. Why is it five, four? Is it, going to be five, seven in a month? What does that mean? And we can see fluctuations of one to two to three points very frequently.

And so I don't have a lot of credence in actually the change in PSA. I think once again, the overall PSA value is your biggest driver and predictor of their likelihood of cancer. Now, if they get diagnosed with cancer, there are certainly data that says that change that you saw before the diagnosis can predict the likelihood of having a more aggressive cancer in there.

But there's not a lot of good data I would say that PSA velocity leading up to a diagnosis has much credence.

Host: So let's say we have a patient whose PSA has jumped to five in my practice. He's a, let's say 62 year old, man. I send him to you. What happens? What happens next?

Dr. Pierorazio: Yeah. So, this has also changed in the last five years where now MRI is our next step and multiparametric MRI, the reading interpretation and utilization of that has increased dramatically over the last decade. And there are a number of level one evidence studies, now randomized trials that demonstrate MRI can improve the detection of not only cancer, but really what we want are those high risk or aggressive cancers. And it really helps as a screening tool to avoid unnecessary biopsies and really target men who have actionable cancers.

Host: I'm glad you brought that up because I had seen that and it wasn't clear to me based on what I was reading, whether or not you were using MRI to sort of help localize for a potential biopsy or really using it as an additional screen as to whether or not to even do a biopsy. It sounds like the latter is true.

Dr. Pierorazio: Well, I think it's both of those circumstances, to be honest with you. And in some patients, you know, your borderline patient with the PSA four

or five with known BPH. It may help you decide whether or not to biopsy. The trick and we're really important statistic that people should take away from this podcast tonight is that they use something called a PI-RADS system, which goes from one to five with the risk of having an aggressive cancer, even with a totally normal MRI, there's still about a 20% chance that there is a cancer underlying, so it doesn't necessarily get somebody out of biopsy, but it does two things.

It helps us with those patients that are on the borderline. We're not sure, or we're trying to avoid biopsy in. And the second thing, we now have the technology in our offices where we can take that and fuse it with our ultrasound machines and actually target regions of the prostate that are suspicious for cancer. And it gives us much higher yield biopsies as compared to just our traditional systematic or kind of random biopsies.

Host: So, how do you do a biopsy? Can you just take us through the, what the patient experiences.

Dr. Pierorazio: Yeah. This has shifted a little bit too in the last I would say couple of years, so. All biopsies are done with a transrectal ultrasound. So, we place a probe that's about the size of a finger in the rectum. And these can either be done under complete local anesthetic or in most of our practice, especially at Penn and at Presby, most of our patients are under sedation, so they're kind of lightly sedated in the operating room, but not general anesthesia. An ultrasound probe gets placed in the rectum to visualize the prostate. Biopsy can be done either transrectally, meaning that biopsy needle can then pass with ultrasound guidance through the rectal wall into the prostate. And now we're really preferring to do most of these biopsies what's called transperinealy. So instead of passing that needle through the rectum, we're passing the needle through the perineal skin, basically that skin beneath the scrotum, and we can target, the prostate is basically right there.

Some people may remember we used to do prostatectomies through the perineum as well. And so that you can really target the prostate really well. And the benefit of doing transperineal or is twofold. First, you get some really nice sampling of the prostate, just technically the way the needles come in, rather than through the rectum.

But the second is the infection rates are incredibly low with transperineal, less than 1%. And in all fairness, you can get an infection rate after biopsy of less than 1% with a good transrectal practice, but it always requires antibiotics. And

now trying to be good antibiotic stewards, we can do transperineal biopsies, achieve the same low infection rates of 1% or less without any antibiotics at all.

Host: That makes a lot of sense, of course, you know, because that's what the bacteria are in the rectum and if you can avoid them. So how many biopsies do you do? How many needles?

Dr. Pierorazio: Yeah, so we still do that systematic or random biopsy. We haven't been able to get away from that because MRIs are imperfect, because we're not great at sampling; there's kind of a perfect randomness to 12 needles of the biopsy typically do six needle cores on each side of the prostate.

And then if we find something suspicious on an MRI, we will typically pass an additional two or three needle passes into each suspicious area. So, on average, our biopsy cores have gone up a little bit. But at a minimum we're doing 12. Most people have one targetable lesion. Occasionally we'll have two. So you'll get anywhere from 12 to 18 cores in general.

Host: So most of us are familiar with the Gleason score as the sort of grading the results of the pathology that you get back. I know you know, it used to be I believe a 1 to 5 scale. Right. And so you would grade the two most significant ones is that right to create the Gleason score.

Guest 2: That's exactly right.

Host: So there's been some change there now, though, right? In terms of how to think about Gleason scores.

Guest 2: Yeah, there is the traditional Gleason score still exists and basically give kind of the quick version. And I'd love to hear how Vivek explains this to his patients as well, too. But Gleason score goes from 2 to 10. We don't see 2's through 5's anymore. Those are kind of historic Gleason scores. So, Gleason 6 describes low risk prostate cancer and the way I describe that is that's cancer that really, it has a low potential for metastatic disease. This is cancer that's not going to kill anybody. When we see a little bit of aggressive cancer, those are Gleason 7's. So 3+ 4 or 4+3 describes the ratio of aggressive cancer to low risk cancer.

And the men, we worry about dying of prostate cancer who are really have aggressive cancer. Those are the 8s, 9s, and 10s, when we're seeing only aggressive patterns of cancer. There's been one other shift because Gleason is

really challenging as a patient and as a caretaker to interpret there's something called Gleason grade groups, which now go 1 through 5.

So at Gleason 6 is a 1, a Gleason 3+4 would be a 2, a 4+3 would be a 3. And so on up to 10 basically. And the idea there is that it may be easier for patients and their families to interpret that a 1 is really low level and a 5 is really aggressive rather than having to interpret 3+3, 3+4, 4+3. What does that all mean?

Host: I'm curious at what point an oncologist gets involved here? Vivek at what point does an oncologist get involved?

Dr. Narayan: Yeah, so I think you know, it, it depends largely on where you're practicing. I think the first point that's worth making is that in most centers and including in the community, the management of prostate cancer all the way through initial screening and diagnosis, through the management of metastatic disease is largely under the purview of urologists.

You know, here at Penn, we have sort of a mixed model where medical oncologists will often get involved anytime systemic therapy is warranted, which I'm sure we'll talk about in a bit. But, here, we also get involved sometimes earlier on in the treatment discussions when a man is on the fence between deciding between different treatment modalities.

So for example, they've heard the radiation pitch, they've heard the prostatectomy pitch and they sort of want an unbiased opinion about the pros and cons of each approach. Sometimes medical oncology will get pulled in to sort of be an arbiter or a third opinion in that decision-making and then certainly we get involved with the administration of androgen deprivation for men with higher risk localized prostate cancers, or certainly in men with unfortunately relapsed or metastatic prostate cancer.

Host: So a biopsy result is going to bring back you're going to kind of, after this additional workup, you're going to be dividing people into three broad categories. The one is they have localized disease a varying aggressiveness based on Gleason score. Right. You're going to have non-localized prostate cancer, that's not fully metastatic yet. And then you're going to have metastatic disease. Is that, how you guys think about it?

Dr. Pierorazio: Yeah, it's a fair summation. If you think about the staging, but I'll tell you often, at the time of diagnosis where basically given a PSA, a clinical stage by rectal exam and a Gleason score. So, the first thing we think about are risk categories and that's the risk of having non-localized or metastatic

cancer, because basically once cancers outside of the prostate, the paradigm shifted a little bit, but we think more about systemic therapies more and less about surgical therapy as monotherapy in those patients.

Host: So let's start with low risk folks. Let's start with I referred to a watchful waiting. You said active surveillance, who fits into that category?

Dr. Pierorazio: Yeah. So, low risk patients are patients with a PSA less than 10, a rectal exam that basically has normal findings, which would be either completely benign exam or maybe a lump or bump on one side of the prostate and Gleason 6 prostate cancer. And these are men in most contemporary urology practices now who are usually not offered active treatment, they are offered active surveillance. And the important difference between active surveillance and watchful waiting at least in the literature and the way we describe it as active surveillance is a process where we're following a patient with the expectation that if something changes, we can intervene and cure them of their cancer, where watchful waiting typically refers to a patient not really a treatment candidate and we're basically following them for symptoms. And our treatments would be palliative in the sense that they developed symptoms or a problem from their prostate cancer. So, we really do prefer that term active surveillance, which implies cure is still there. We're just following you in case we need to employ our treatment strategies.

Host: And how do you follow them?

Dr. Pierorazio: Yeah. So typically it's serial PSA tests, MRIs and biopsies. There's evolving strategies to do this, but in general, the paradigm for active surveillance, a man gets diagnosed with Gleason 6, prostate cancer, if they haven't had an MRI, we get an MRI in short term.

And the way I describe active surveillance is there's two reasons men come off active surveillance it's either because there was a more aggressive cancer underlying that the initial biopsy missed, or because they're a 55 year old man who developed a prostate cancer. Even though it's low grade now they still have the same risk factors that can allow them to develop a more aggressive prostate cancer in the future.

So the first thing we do is rule out that there's an underlying prostate cancer. We do that with MRI and what we call a confirmatory biopsy. That confirmatory biopsy doesn't need to happen right away. Typically we do that within 12 to 18 months of the initial diagnosis. Once we establish that there's no more aggressive underlying cancer, we'll check their PSA every six to 12 months, we

will do MRI every year to every two years based on PSA kinetics. And then we try to get biopsies out as far as four years based on some pretty good literature, but I'll tell you most patients often end up getting a serial biopsy somewhere in the range of two to three years after the initial diagnosis.

Host: Because of some change in their PSA or symptoms or something like that?

Dr. Pierorazio: Exactly. Usually a change in PSA is the biggest driver here.

Host: So that's the localized prostate cancer population and regarded as low risk, that'll get active surveillance. Let's step up from that so that the next higher risk category are higher Gleason scores, I assume. Right.

Dr. Pierorazio: Yeah. So Gleason 7 basically bumps us into intermediate risk. So now, if a man has a PSA between 10 and 20, if they've got a Gleason score 7, they are intermediate risk prostate cancer. And lay person way I described this and as a simple surgeon, I think it works pretty well too, is that men with intermediate risk prostate cancer have cancer that needs to be treated in a sense that if we don't treat it, it could limit their longevity. However, it is often cured with single modality treatment and we'll get into treatments, but basically prostatectomy or radiation therapy should offer them a cure in the vast majority of men.

Host: Let's come back to that in a minute. Because going into those treatments is going to be an important discussion. Let's go then to step up from that. So a patient who has high risk prostate cancer.

Dr. Pierorazio: Yeah. So now these are men with a PSA greater than 20, their rectal exam, or their MRI may indicate non-localized prostate cancer, or locally advanced meaning prostate cancers growing extra prostatically or into the seminal vesicles, the glands next to it, they potentially have enlarged lymph nodes, that's all clinical staging or on Gleason score, they have an 8, 9 or 10, and this high-risk group is high risk for a number of reasons. They're high risk because they could die of prostate cancer. This is cancer that could affect their longevity. And in addition to that, we can offer cure or control of this disease, but it often requires multimodal therapy.

So you're often looking at radical prostatectomy plus radiation therapy at some point or radiation therapy with androgen deprivation or some other systemic therapy, somewhere in their lifetime to keep this disease at bay.

Host: So the intermediate risk folks, as you had said, can be treated with one modality and that could be curative. But the high risk folks are going to require more than one modality. And those are the folks that you'll be talking with Vivek about options.

Dr. Pierorazio: Absolutely. And just to be clear, obviously there's nuance to this. We're putting people in, broad categories and that's why it's important to go to a place or go meet with someone who has an idea of nuanced care because listen every patient's a little different and they don't necessarily fit nicely into these bins, but these are the general categories that we think about.

Host: Phil theres another sort of veil that we as general internists, I think don't get to peek behind that much. And that is, this whole thing with radical prostatectomy or with prostatectomy generally, and the different ways. And then also I want to get both of your opinion on the different modalities of radiation therapy, but let's talk about prostatectomy for starters.

You know, of course my understanding there was an old surgery a radical prostatectomy had different approaches. But there was that one thing. And now then there was laparoscopic prostatectomy. Then there was robotic prostatectomy. And can you help us distinguish between those three options and tell us what you're doing now?

Dr. Pierorazio: Yeah. So, to be honest with you, the operation is the same and a radical prostatectomy means removal of prostate and seminal vesicles with the intent of cure of cancer. And it's radical because the entire gland is removed and there's something called a simple or total prostatectomy, which is done for BPH.

But the idea is that the urinary and sexual systems at this junction are completely disconnected and put back together again. The traditional approach was through an open incision. It is now greater than 85% of the radical prostatectomies in this country are done robotically. And all of my prostatectomies now are done that way. I think the vast majority of the prostatectomies in the Penn System are done that way. And the reason is it's easier on the patient and it's easier on the surgeon. And I think time has born out that the oncologic outcomes are basically equivalent. It's not necessarily a cancer benefit to doing a robotic surgery, but with experience and someone who knows what they're doing, and who's done a lot of surgeries, the oncologic outcomes are equivalent, but the benefit is really in operating room, convalescence, in and out of the hospital either same day or 23 hours, what's called a 23 hour stay or an overnight stay. People are up on their feet walking

immediately, and it's a much easier softer recovery than it was from the traditional open surgery.

Host: And what do you tell your patients in terms of both cure rates, but side effects. How do you prepare them for, I mean, we know it's the incontinence and the erectile dysfunction is the two main issues that people experience long-term.

Dr. Pierorazio: Yeah. So, the cure rates are really determined about with their pathology. So we know based on low, intermediate or high risk, what the chance of cure with surgery is kind of generally or radiation treatment. There is a little bit of nuance based on what it looks like when then when it comes out and under the microscope. And I tell people that's one of the benefits of radical prostatectomy is we get the whole prostate out. We're able to look at the entire thing under the microscope, so we know exactly what we're up against, and that helps us guide future treatment decisions. But the oncologic outcome's are pretty good or actually excellent. So for men who go to the operating room with low or intermediate risk, low or intermediate risk disease, their cure ate should be basically 95% or better. Obviously that rate drops for men with high-risk disease with, surgery as monotherapy, but as you bring up the big downside to surgery, is it surgery and with robotic technology with advancements in anesthesia, operative complications are really low.

These are traditional operative complications like bleeding, pneumonia, blood clots. These things rarely happen. They certainly do. And they certainly can, but those are less common. The two big things we do worry about as you alluded to are erectile dysfunction and urinary incontinence. And erectile dysfunction is based on a number of things. The first one is really where men start going into the operating room. And so if men don't have great erections or sexual function going into the operating room, they are not going to maintain good sexual function coming out of the operating room.

And those are the men that we counsel ahead of time that listen erectile dysfunction and sexual function is a really important part of recovery. And if it's important to you and it's important to your significant other, this is one of the easiest things we fix in urology. And in fact, I have colleagues who just, as my practice is completely devoted to cancer patients and cancer surgery, their practices are devoted to quality of life. And one of the quality of life treatments is the treatment of erectile dysfunction. We can make it work if you have the interest or your significant other has the interest, that can be corrected. The bigger challenge is often urinary continence.

And once that is really age dependent, younger men, much more likely to recover their continence after surgery than older men. And it's not necessarily a fitness factor, but you can think about it. Listen, you know, when we were 18, 20 year olds, if we were playing sports and we rolled our ankle, our ankle is going to recover and will do it in a fairly reasonable amount of time.

But you can imagine, as you get into your fifties, sixties or seventies, you may not recover as quickly and you may not actually ever fully regain function of that ankle activity like you did when you were 18. Well, the same things control our urinary control, its blood vessels, muscles, nerves, and it's our ability to recover and regain that control that can be a challenge after surgery.

Host: Patients who have long-term incontinence, they need to be taught to self catheterize. How do they end up like managing that?

Dr. Pierorazio: Yeah, it's often the opposite. It's leakage of urine and the most common phenomenon is what's called stress urinary incontinence. Women, as they age, get very familiar with this concept. This is leakage of urine with cough, sneeze or abdominal exertion. And just to kind of clarify, kind of age-related outcomes for most men in our practice. And we know this by following our outcomes. Most men in their fifties, about 95% of them will have good urinary control at the end of a year of recovery after surgery. For men in their sixties, it's about 90%. It can get a little bit lower for men in their seventies, but those are the general numbers we describe to people and was commonly said, it's stress incontinence.

So it's leakage of urine coughs, sneeze, exertion. Most of that is manageable with a pad or a diaper, depending on kind of how much leakage and some of it's just what we call kind of social incontinence. Meaning if you didn't wear a pad, your pants would look wet and you would be embarrassed, but you're not soaking throughout the day and you can often manage it.

But occasionally there are men who have real problematic leakage after surgery, and there are a number of procedures or surgeries that can be done to tighten things up for lack of a better term. There's something called slings, which will basically create a resistance mechanism in the urethra to help provide a continence mechanism or something called an artificial urethral sphincter, which is a prosthetic device that surrounds the urethra and will actually clamp it off to hold urine in. It's activated with a pump in the scrotum that will release that cuff, allow urine to leave the bladder when somebody has sensation that they're full and then it will fill back up over the course of 30 seconds to a

minute and provide full continence after that. So there are solutions, obviously not ideal to think about additional operations.

Host: It sounds like incontinence is a bigger problem than erectile dysfunction.

Dr. Pierorazio: Obviously, some men would argue with that.

Host: A harder problem for you to solve.

Dr. Pierorazio: Yeah. yeah. It can definitely be more challenging. And as prostate cancer treatments have shifted from we saw a lot of men with low risk, 10-20 years ago, and they were getting operations now to men with high risk disease that are going to require multimodal therapy.

Multimodal therapy adds up to toxicities, right? So, erectile dysfunction is a real problem after surgery and radiation or after radiation and androgen deprivation to be honest with you. So, we recognize that those men are gonna need help with erections and sexual function moving forward. So, in the operating room, we are keenly focused on their urinary continence and trying to preserve mechanisms, anatomically that are going to give them the best chance of holding onto their urine moving forward.

Host: So, we've talked about active surveillance and we've talked about prostatectomy and now let's turn our attention to radiation therapy. I'm actually gonna Vivek I'm gonna, shift my focus to you a little bit in terms of, if you have one of these patients who is sitting in your office and they're considering radiation therapy, how do you approach that discussion? What do you tell them? They should expect to now in my mind, I also have questions about the different modalities of radiation therapy as well. And what's your sort of elevator pitch to them?

Dr. Narayan: Yeah. So, as Phil described for men with intermediate risk disease, or for men with high risk disease, both of which warrant active treatment, radiation therapy is a treatment modality that can achieve cure for both sets of risk stratified groups. For intermediate risk disease it can be given with, or without androgen deprivation therapy, but almost certainly for high risk disease in the vast majority of cases, we'll strongly advocate for the use of long-term androgen deprivation along with radiation therapy. One of the advantages of radiation therapy is that it's not surgery. And so some of the sort of surgical risks that Phil described, thankfully are not present with radiation therapy. And so even men with medical comorbidities, which are common, as prostate cancer population is mostly men in their late sixties, early seventies, can still undergo

radiation therapy. And so certainly even men into their eighties and even nineties at Penn have undergone radiation therapy for prostate cancer. The downsides are that as Phil alluded to you don't necessarily get the full pathologic picture from radiation therapy because the prostate still remains intact.

And so you're limited to the risk stratification and the information that you've gleaned from the biopsy and the initial clinical staging, as opposed to a surgical pathology specimen at the time of surgery. And then I think another important downside of radiation therapy that's important to highlight is that especially as we move to sort of intermediate and higher risk prostate cancers, of course, what that means is that there is a higher risk of a recurrence of prostate cancer, despite local therapy on the prostate, be it surgery or radiation therapy. And so in the case of surgery if a man is unfortunate to have a PSA recurrence or relapse of prostate cancer, there's often a standard pathway of using things like salvage radiotherapy to try to eliminate any residual prostate cancer cells if they have been confined to the pelvis or the prostate bed. With radiation therapy, there are still salvage modalities that can be used on an intact prostate, but it does become a little bit more complicated because as Phil was describing, when you add up these different local treatment modalities. So whether it's surgery followed by radiation or radiation followed by other salvage maneuvers on now in a radiated prostate, those risks of quality of life toxicities unfortunately go way up.

Host: Radiation therapy. Can you guide us through a little bit, there's sort of bead placement, radiotherapy, brachy therapy, right? And then there's also Penn does proton therapy. Can you help us distinguish between those options?

Dr. Narayan: Yeah. So I think first to start with the brachytherapy. So these are interstitial implants that admit localized radiation therapy you know, by and large this is used for sort of very low risk or low risk prostate cancer, oftentimes men who could now in more contemporary management be followed with active surveillance.

And so I think for the most part, when we're talking about radiation therapy for the treatment of prostate cancer, we're really talking about external beam radiation therapy in the vast majority of cases. And so this is typically delivered through photon radiation at most centers in the Western world.

Here at Penn, there is the option in some cases for proton radiation therapy and the difference there is I'm certainly not a radiation oncologist, but the way I describe it to patients is a difference in the particle and the energy of the particle

and the distance and stopping kinetics of the particle as it travels through anatomic tissues. So in the case of photon radiation therapy, these are generally linear beams that travel into the tissue through the cancerous tissue and then exit out the back of the cancerous tissue. Whereas with proton beams, there is what we call sort of a stopping distance or a limit to the distance of the beam and particle itself, such that you're hopefully avoiding some of the exit dose of radiation therapy on the back end.

And so there's some theoretical practical advantages in terms of sparing normal tissue toxicities by using something like a proton approach. I think at most centers now that are using contemporary radiation modalities for prostate cancer, they use what's called conformal techniques, even with sort of external photon based radiation.

So one example of this is things like IMRT or intensity modulated radiation therapy. And again, my sort of simplistic way of thinking about it is kind of using these linear beams, but in three dimensions, to sort of more conformally treat to the anatomic prostate gland and the areas of interest while trying to limit the dose to the surrounding tissues. And in the case of prostate cancer, it's really the bladder and the rectum that are at risk.

Host: And so that two of you regard prostatectomy and radiation therapy for intermediate risk patients to be roughly equivalent, it just depends on the balance of the factors that you've described.

Dr. Narayan: Yeah, think that's fair. So, I think one of the limitations of the prostate cancer literature is that it's really hard, as you can imagine to do proper randomized trials, randomizing patients with cancer to surgery or radiation therapy. We all have our internal biases about which we want to pursue.

So to, randomly allocate people, it's a tough study to do, but I think all of the evidence that we do have, seems to indicate that both for intermediate and high-risk disease, the outcomes are largely equivalent. It's more sort of how you're going to get there. And what are the toxicity differences and the co-morbidities that may be at play when trying to make that decision between the two treatments.

Dr. Pierorazio: Yeah, I couldn't agree more with that statement. I think that's spot on and exactly the way we think about it.

Host: So when do we start thinking about systemic anti-androgen therapy Vivek?

Dr. Narayan: So I think the main area, you know, still focusing on clinically localized prostate cancer, is certainly these men with high risk prostate cancer. So, these are men with high Gleason scores, so 8 or above, really high PSA values or with a clinical imaging, such as an MRI or digital rectal exam that's indicating disease outside of the prostate. I think it's important to note that of all the men who die of prostate cancer in the United States, and by the way, prostate cancer is still the second leading cause of cancer death in the United States; the vast majority of those men who die of prostate cancer initially presented with the high risk localized prostate cancer.

And so that just sort of illustrates the point that these men are at risk of potential dying of prostate cancer when they present with high risk localized disease. And so what that high risk designation indicates, there's again, a risk of potential microscopic disease outside of the prostate.

And therefore there may be limitations to sort of just focal therapy, whether it's surgery or radiation therapy on the prostate itself. And so in the case of radiation therapy, we will give up to two years of androgen deprivation therapy. So, these are typically GnRH agonist therapies to suppress testosterone levels during the course of radiation therapy and for a prolonged period after the radiation therapy, up to two years, and that's based on high-quality level one randomized evidence indicating that men actually live longer and have less prostate cancer specific mortality with the use of this long course of androgen deprivation therapy in conjunction with things like radiation therapy.

In the case of prostate surgery for high-risk prostate cancer, we don't have that same evidence. So that's one of the advantages of prostate surgery is to avoid androgen deprivation therapy for the treatment of localized high-risk prostate cancer. But of course, because it's high risk disease, as Phil said, there's a high likelihood that you made that need multimodal therapy, whether it's subsequent radiation therapy and or androgen deprivation therapy to manage the disease.

Host: For the patient who presents with metastatic disease, and I think you noted it was 5%. I believe. These folks, the only modality is anti-androgen therapy, right? There's no local options, right?

Dr. Narayan: Well, that is also evolving. So, certainly the fundamental therapy is androgen deprivation therapy. And for men who present with metastatic disease, we know that that's generally worst prognostic group of men who present with metastatic disease. So, as opposed to men who five years ago had a prostatectomy and then some salvage radiation therapy, and then now are presenting with relapsed metastatic involvement that sort of latter description

often will fare much better prognostically compared to the man who walks in the door with a bone scan showing metastatic disease of prostate cancer. And so in those men with a de novo metastatic presentation of prostate cancer, certainly androgen deprivation therapy is the fundamental approach. And that's typically lifelong continuous therapy. But even in those cases, in men who have what we call a lower burden of metastatic disease, so for example, a man who has a CT and a bone scan that shows three or four bone metastatic lesions, no visceral metastases and if they still have an intact prostate, that's been untreated. We will offer them radiation therapy to the prostate in addition to their systemic androgen deprivation, because that's been associated with a survival benefit in that particular population.

Host: We see these patients back in our practices who are on androgen deprivation therapy of some form. I know there are some things that we then need to look out for because they have low testosterone levels and so forth. What are the, some of the things that of primary care internist needs to know?

Dr. Narayan: Yeah, so I think androgen deprivation, it's really interesting to think how profound of an impact testosterone or androgen signaling has for prostate cancer. So, even in that patient, I described who walks in the door with diffusely metastatic prostate cancer, we know if we start them on testosterone lowering therapies, we can have a profound impact on their symptoms, disease control, and ultimately survival from prostate cancer.

But it certainly comes with consequences and it's physical or physiologic consequences, but also psychological consequences in terms of mood changes, emotional lability, and really sort of a man's perception or self-identity all can be effected by profound suppression of testosterone. I think from a primary care standpoint, important things to note are that certainly what patients will complain about are things like hot flashes and loss of libido.

Unfortunately, we don't have great tools to really circumvent those toxicities. But I think as providers that give androgen deprivation, what we really care about and need to monitor for is the metabolic changes that occur when you suppress testosterone so profoundly and for such a long period of time, or, you know, oftentimes years for these men.

And so in, this case, when the testosterone is suppressed, we know that that can cause weight gain and it tends to be weight in the wrong areas of central adiposity redistribution of weight. There can be muscle loss or sarcopenia, certainly bone mineral density loss, especially with prolonged androgen deprivation therapy.

And along with all of these metabolic changes, we certainly worry about the risks of glucose intolerance or new onset diabetes, dyslipidemia. And of course, all of these things may play into an elevated risk for cardiovascular disease or events. And so I think those are the things we really try to partner with primary care physicians to monitor and help manage over the course of prostate cancer treatment.

Host: So someone could be on androgen deprivation therapy for at least five years, 10 years, even further, right?

Dr. Narayan: Yeah. So, you know, I think this is also an important point. So, even in men who present with metastatic prostate cancer or stage four prostate cancer, we think in terms of survival of many years. These competing health risks, I think are still critically important in this population. You know, this is different from pancreas cancer or lung cancer or some other aggressive cancers, that you know when metastatic, unfortunately the treatments may not be as effective as things like androgen deprivation for prostate cancer and therefore the prognoses, unfortunately aren't as long as they may be for a metastatic prostate cancer. And so, even for the men with metastatic presentations, we think in terms of median survivals of five, or sometimes more years.

Host: So we're getting tight on time now. And I wanted to wrap it up, but I first of all, I want to thank you both for being here, but I also, we often ask our experts to leave us with a thought for the primary care community, in terms of any closing thoughts, things that you think are important for everyone to know that maybe you haven't had a chance to say.

Dr. Pierorazio: Yeah, I guess I can start. Prostate cancer is incredibly common and there's a lot of nuance to the screening and management. So, the first thing I would say is reach out to us. We are here for you guys. We are here for your patients. This is what we really enjoy doing. So we're happy to kind of walk you and your patients through this.

And for patients who are diagnosed with prostate cancer, I would make, I make to all of them, the recommendation go to someplace that treats a lot of prostate cancer. Go to someplace that treats a lot of prostate cancer really well, and go find someone that you feel comfortable with. This is a really common disease. There are a lot of people who can treat it well, and you shouldn't feel kind of strong, armed into any treatment that you or your patients are not comfortable with. And the biology of this disease is often much that you can seek out second, third, fourth opinions. That's totally okay. And if you ever want to do that we're happy to see your patients at Penn Urology. It's what we love.

Dr. Narayan: I would echo everything that Phil said and just sort of maybe you know, restate the points that the diagnosis of prostate cancer does not always commit to treatment. And what I love about prostate cancer is that treatments there's many different nuances to it. There's many different treatment modalities. And even in the sort of more advanced stages, the medicines that we use, there's many different ways in which we try to utilize them to balance great oncologic outcomes, but also quality of life outcomes. And so I think it's a fast moving and evolving field. And I think you know, certainly the outcomes are getting better and better.

Host: Well, thank you both so much. I really look forward to having you both on again, to talk about another urogenital malignancy. I have a special sort of interest in renal cell myself from some personal family experience. And I'd love to have you back at some point to talk about that.

Dr. Pierorazio: I'd be absolutely honored.

Dr. Narayan: Thanks so much.

Host: So thank you everyone for joining the Penn Primary Care Podcast. Please join us again next time.