

Chuck Ryan:

I am Chuck Ryan. I am the president and CEO of the Prostate Cancer Foundation and your host tonight and delighted to be here. While you're all getting started, going to talk a little bit about the Prostate Cancer Foundation. We are a foundation that funds research across the world. Our mission is to reduce the death and suffering from prostate cancer. We support transformational research to accelerate this progress, and we fund teams of scientists, young investigators, and we seek to bring the brightest and the best young and old investigators into the field and into the mission of reducing the death and suffering from prostate cancer. We are the global public square of prostate cancer. In addition to funding research, we do communications efforts, educational efforts like we're doing tonight, and patient support, which I think is also something that we are doing tonight.

I encourage you all to visit our website, PCF.org, where we have resources for all of you on various aspects of this disease, whether it's understanding the disease, whether it's understanding how the disease may affect your specific population of individuals, download our patient guide, access previous webinars, join an online support group, and become part of our growing community that is global for prostate cancer patients here in the global public square of prostate cancer. Tonight I'm thrilled to have two guests who are joining me. We're going to change the format a little bit and what we've done in the past is we've had two guests that I've spent a half an hour with each of them. Today we're going to have both of our guests joining us for the full hour because it's a really multidisciplinary set of issues that we're going to face.

First, I'm delighted to introduce Dr. Ashley Ross, MD, PhD from Northwestern. Dr. Ross is an associate professor of urology with an expertise in prostate cancer and in particular, all of the aspects around early prostate cancer detection, screening, biopsies, treatment of localized disease and novel diagnostics and therapeutics across the gamut of localized prostate cancer. Dr. Ross, thank you so much for joining us. I think you can switch your camera on and we're going to get started here. So welcome, joining us from Chicago tonight.

Dr. Ashley Ross:

Thanks so much for having me.

Chuck Ryan:

Thank you for being here. My second guest is Dr. Paul Nguyen, MD, MBA from Dana-Farber/Harvard Cancer Center. He is a professor of radiation oncology, Harvard Medical School. He's also the vice chair for clinical research at the GU disease cancer and the GU disease cancer leader for radiation oncology at the Dana-Farber Cancer Institute. He also has a clinical focus on personalized treatment for men with localized prostate cancer using all of the tools that we can today, which is genomics, clinical factors, et cetera. He's also got a deep expertise and thoughtfulness in health services research. Paul, great to see you. Welcome.

Dr. Paul Nguyen:

Thanks for having me, Chuck. I'm excited to be here.

Chuck Ryan:

So rising PSA is one of those conditions that I as a medical oncologist also face in my practice. In fact, I think it's the most common source of referral that I get as a medical oncologist. And Ash, I'm going to start with you. Let's go back before we tackle the controversies and the challenges of what to do when

your PSA is rising after treatment. Let's talk a little bit about who, when they're facing their initial treatment decision, faces the greatest amount of risk that they would confront this problem after treatment. In other words, who's at the greatest risk for relapsing? How do you consult patients about this?

Dr. Ashley Ross:

It is a great question. Essentially, what we have to realize is as we've progressed in our understanding of prostate cancer, for men who have low risk prostate cancer, we are usually surveilling those men like watching their disease. And so really taking men to treatment where we think their disease is important to treat, can cause problems that they aren't treated. In that context, we are usually thinking that about 30 to 50% of them will have some sort of disease relapse and we often call that biochemical recurrence throughout their journey. Now, as you mentioned, it gets modulated by two things. One, the risk of the initial disease, and second is that man's health and age. The longer you live, the more chance you have for recurrence. The riskier the disease, the more chance you have for recurrence.

Initially, the risk categorizations that we often think about as providers, the National Comprehensive Cancer Network classifications, the American Urologic classifications were based initially on metrics that were put forth by a radiation oncologist, Dr. D'Amico, when he was looking at what things can define your risk and what was your risk of needing more treatment or having recurrence after treatment, actually. Men at higher risk by the standard classifications, higher Gleason scores, higher initial stage, meaning with your fingers like this, higher PSA levels. And now in the era of molecular medicine, higher decipher scores and some other metrics too. These things can tell us that your risk of recurrence after initial treatment is going to be elevated.

That is important in the initial determination of what you want to do for treatment. And additionally, just to level set on, you might be cured by step one, but you might need a plan two, three, four, and et cetera. One final thing before I turn it over is, I think the patients have to realize in some other cancers, it's very common to give cancers a one two punch, et cetera, but for the prostate, because of where it is near these functional structures around erectile function, urinary control, et cetera. And because we have this excellent biomarker in the PSA that was first actually FDA approved for following men after treatment, we can sort of do things in a sequential fashion. But long-winded answer, but essentially disease characteristics put you at more or less risk of recurrence and we should fully expect that 30 to 50% of our men, whether they're starting with surgery or radiation, might have recurrence of their disease within their lifetime.

Chuck Ryan:

A lot of great points in there. That 30 to 50% translates into, I've told patients in the past, 30 to 50,000 cases a year of men who are experiencing relapse after their initial treatment. We're going to talk about how to subdivide that population into those who need intensive therapy versus maybe no particular therapy. But Paul, let me ask you, so somebody undergoes surgery, their prostate's out, the PSA should be gone, and where is the cancer, and how do you know where it is, and how do you know where it isn't at this point?

Dr. Paul Nguyen:

It's a real dilemma, Chuck, I think. And it's a very natural question, which is that if you had surgery and you had the whole prostate removed, then how can you possibly have any more prostate cancer or any more PSA in your body and what's going on? In theory, the cancer could be coming from one of two places. It could be that at the time of surgery there was accidentally a little bit left behind or a little bit

that grew just beyond where the surgeon could cut or see during the procedure. That happens sometimes, but I think more commonly what we see is that there's a cell or a number of cells that have made it out of the prostate even before the time of the surgery. So even before the patient ever gets on the operating table and those cells, they can travel through the bloodstream, they can be hidden in the pelvic lymph nodes or they can be in the area around the prostate where the prostate used to be.

It can be a dilemma to try to figure out where these cells are. And I'm sure that's something that we'll be talking about a lot today is when somebody has a PSA that's detectable after surgery, is trying to figure out where those cells are, where they're hiding, and how do we treat them. As a radiation oncologist, we think a lot about that because we have to design our radiation fields, we have to figure out where those cells are hiding so that we can try to target them in whatever area we're aiming at. The vast majority of the time as a radiation oncologist, we can't see those cells that we're aiming at. And so we just have to go where historically we know that cells tend to hide and usually the most common place where those cells hide is at the anastomosis, which is where the surgeon sews the neck of the bladder back to the penile urethra. That's a very common place.

The second most common place would be on the back of the bladder. Just on the back end of the bladder where the prostate used to be. And now what we've been seeing more and more is that sometimes disease can make it to the lymph nodes even if we don't see anything on a normal scan. One nice thing that I think you're alluding to Chuck is that we actually have imaging now that's gotten a lot better compared to what we had even just three years ago, which is PET imaging. In particular, we now have Fluciclovine PETs, which came out around 2015. And most recently we have PSMA PETs, which came out in the United States in the last couple of years, although it had been available in Australia and Europe and elsewhere for many years at this point.

I don't know if you want me to get into that now, Chuck, but that is a scan that we can use to sometimes detect these cells at a reasonably low PSA like 0.3 or 0.5, whereas before we would have no hope of seeing any of these cells on a conventional scan, like on a bone scan or a CAT scan.

Chuck Ryan:

It's really revolutionized how we think and how we conceptualize this disease. I do want to come back to the scans, we'll dive a little bit deeper on those in a few minutes. Before we get into scans and true cancer relapse, Ash, a question that comes up sometimes is, is all PSA cancer after the prostate's been removed or are there situations where you can have a detectable PSA and you don't have any prostate cancer?

Dr. Ashley Ross:

It's a great question. As Dr. Nguyen said that essentially there's a couple different things that can be causing your PSA to rise. PSA is made by the prostate and by prostate cancer cells. The PSA could be prostate cancer cells, whether they're within the prostate bed, in the pelvis or systems in the body producing that PSA. Or they can also be benign non-cancerous tissue that was left behind at the time of surgery, commonplace being under the bladder neck, at the urethra where the surgeon was trying to preserve structures and maybe some cells were there. Now another good point around this is that more recently we've been using ultrasensitive PSAs. Not all providers use it, but the American Urological Association and other associations still benchmark PSAs of 0.2 after surgery with biochemical recurrence. But a lot of us know that the old assays were accurate at 0.1 for sure.

And now these newer assays are reading out at values that are 0.01 or even sometimes less than that. The question is, this is the third point of, are all PSAs from something as you look at these ultrasensitive

values, values that are 0.01, 0.02, can sometimes be in the area of actually noise in the assay. False positives that are analytically false positive or perhaps the patient is even, and I don't want to get into the specifics here, making a human anti-mouse antibody or something like this that's interfering with the assay and giving you the spurious positivity. That kind of rolls into a question we may get into later or now, which is, "Well, we can detect these low PSA levels, what PSA is important?" And usually in my practice, I'm not pulling the trigger on more therapy until the PSA is consistently 0.03 and above. But those are the three ways that you can get it, spurious at these really, really low values, it's benign tissue, or what we're most worried about, it's prostate cancer.

Chuck Ryan:

I did not have human anti-mouse antibody on my bingo card for tonight, so that was a good one. Tell me though, do you have a cutoff point where you say, "This is potentially benign and above this we're going to treat in all cases"? That's, I think, the first part and the second part is, perhaps a little bit more nuanced is, our patients now can get access to their medical records and many of them are reading their pathology reports and they're reading their surgical reports. Is there something that they can see in their surgical or their pathology report that would make them think that perhaps their PSA is going to rise over time?

Dr. Ashley Ross:

Absolutely a great question. I think actually to the most part, expanded access to the patients for the medical record is a very, very good thing, and then to just understand that information. The first thing is, as Dr. Nguyen was saying before, adverse pathologic features are a sign that your disease might be of higher chance of recurrence. What are those adverse pathologic features? Those are either that the disease has extraprostatic extension, we'll see in the report that there is extraprostatic extension. That means that the prostate has a capsule around it and that your cancer has figured out not only how to live in the prostate, but it's also figured out how to live outside of the prostate. And that means that it can live kind of in the surrounding fat from the prostate and stuff like that.

That can be a sign that you might be at more risk of recurrence, particularly seminal vesicle invasion. The seminal vesicles are like the ears in my head if my prostate's my head, they're sort of attached to my head. They're not necessarily originating from my head. And actually the seminal vesicles on the prostate have a different embryological origin during human development than the rest of the prostate. In essence, they're almost closer to another organ. Having seminal vesicle invasion is a sign that your cancer learned to grow not only around the prostate but a little bit further from home, and that can be a sign of having an issue. Patients with microscopic lymph node positivity, which we'll get into later, that's also a sign that they might be at higher risk. And then finally having those and having a positive surgical margin. That means when we take the prostate out and I give it to the pathologist, the first thing they do is ink the outside of it and then they even see if they have a positive margin or not.

The reality is for some patients with extraprostatic extension and a negative margin, they may never have a recurrence, for ones with a positive margin and extraprostatic extension, it might be more likely. Looking at the pathology report, the patient can look at it and say, "Well, I may be at higher risk." And then we talked a little bit about molecular stuff too. I often will use a decipher score. Decipher scores that are higher might also mean that you're going to have a chance that you'll have a recurrence. Then the question is, "How do I level set this with the patient?" And this will be something that I think Paul will talk about at much more length, but in the past we used to just say, "If you have adverse pathologic features, maybe those guys are going to inevitably have a recurrence. We should just give them radiation immediately. As soon as they recover their urinary control, give them a radiation."

And then more recently in the last couple years or so, there's been three large clinical trials that have level set us on, when do we pull the trigger? And it suggested that for the majority of patients, we can wait until the PSA reaches 0.1 or 0.2 to pull the trigger on the radiation without losing much ground. But there's some patients that have a more aggressive features, higher Gleason grades, Gleason grades 4 to 5, those are your sums at equal 8 to 10 that have seminal vesicle invasion that I mentioned can be a sign that the cancer can live other places. Obviously the ones that have lymph node positivity and ones with those higher genomic scores, then I will want to send them to the radiation oncologist much earlier.

Usually when the PSA is consistently above 0.03. If they don't have those features, Gleason sum is 7, T3a a disease meaning extraprostatic extension but no semi vesicle involvement, I'll often monitor them till they get to 0.1 and then I'll send them to my radiation oncologist. There's different thresholds and the patients should know that there are patients that hover at a PSA level, we'll talk about doubling time later, a PSA level that's kind of like lower than 0.1 for a long time. There's some patients that take a long time to go from 0.1 to 0.2. But what we don't want to miss is the opportunity for cure.

And the curability when I send them to Dr. Nguyen, is going to be highest when the PSA is lower. And he's talking about PET imaging, et cetera. I find that that's a very useful tool for after you've had full pelvic therapy but I'm not usually waiting till the PET is positive before I send them to my radiation oncologist. I'm trying to get them into Paul's hands when the PSA is very low, the earliest points they can start thinking about what does this mean for their radiation.

Chuck Ryan:

You've moved us ahead in the conversation quite a bit, which is great. You've basically pointed out that the first step for a person who's had a surgery after their pathologies come back and they see a rising PSA, the next therapeutic consideration is radiation. Paul, before we get to radiation and the techniques and how you do it, walk us through what Ash alluded to about PSA doubling time and what that means in terms of patient's risk.

Dr. Paul Nguyen:

Actually I hope it's okay, I was just scanning through the question and answers. I saw a couple of folks ask the same question about Ash's comment that, "Do you pay attention to the PSA when it hits 0.03? Is that what you said or is it 0.30?" Couple people asking that.

Dr. Ashley Ross:

For me, I pay attention once you're at 0.03. And that doesn't mean that I necessarily think they absolutely need more treatment at that point, but say they've been at less than 0.01 for years and now we've been checking the PSA every year and it's year four and there's 0.03. I'm certainly going to change the cadence that I'm watching. I'd be interested in your thoughts, Paul, about PSA doubling time in the ultrasensitive range. But that's when I think it's no longer a spurious value. Something is going on, whether it's benign tissue regrowing or there's cancer regrowing, that's when our antennas go back up. And in my patient population, you're back on an every three month cadence. And if you're going 0.03, 0.05, you're getting probably a referral that you may inevitably need radiation to my radiation oncologist.

Dr. Paul Nguyen:

Thanks, Ash, for clarifying that. I'm pretty similar. I would say that I've been telling my patients that up until 0.04 or so, I can sort of suspend disbelief and think that there may be nothing significant going on

here. But once I see a 0.05, 0.06, I really started thinking, "We may be headed someplace and we need to anticipate needing to do something." But I agree with you, I would not treat anybody until 0.1, at least based on the trials. But it does get to Chuck's question about PSA doubling time. We can calculate a whole bunch of parameters as we're watching PSAs go up to try to figure out, is this increase significant? Is this something that we need to worry about? And certainly the rate of rise of the PSA in general gives us some information. I think that as I've been kind of taught to think about this, PSA doubling times have a lot of value once the PSA gets out of the ultrasensitive range.

Let's say your PSA is 0.3 and it goes up to 0.6 within three months, that's a doubling time of three months. That's meaningful. But when your PSA is like 0.01 and it goes to 0.02 in three months, that's not really as meaningful or possibly not meaningful at all. In terms of doubling times, I think as Ash's called out Dr. D'Amico and others have certainly thought about this, but as the PSA doubling time gets shorter, meaning let's say less than six months or even less than three months, then the likelihood that this cancer is an aggressive one, one that's trying to perhaps even metastasize goes higher and higher. Whereas if the doubling time is very slow, such as it takes more than 12 months for a PSA to double, then usually those aren't as aggressive. It doesn't mean we don't have to deal with them, but there's something going on.

Chuck Ryan:

Paul, I'm taking a task on this because Anthony D'Amico wrote a paper, I think it was in about 2005, 2004, where he asserted that a PSA doubling time of three months or less meant that death from prostate cancer exceeded all other causes of death over time for those individuals. My question is, do those numbers hold up in the current era? Because that's now 20 years ago, perhaps. And those patients who were treated and were followed up before he published that paper were treated in the 1990s. Do we still think of PSA doubling time as such a dire thing when it gets down to be such low or such rapid levels, number one, and a number two is, how do you use PSA doubling time as a treatment criterion or as sort of in your decision algorithm as far as who to treat, what to treat, when to treat, and where to treat them?

Dr. Paul Nguyen:

Thanks, Chuck. I'll take a stab at the first question, but since you're the medical oncology expert, I will ultimately defer to you and love to hear what you have to say about it. But Anthony D'Amico's paper back in 2004, 2005. I do remember it saying, basically claiming that a PSA doubling time less than three months is a surrogate for prostate cancer death, meaning that you will die of prostate cancer. As you point out rightfully so, those patients were treated in the 80s, in the 70s and the 90s. And so there weren't many treatments at that time for recurrent disease like we have now. I don't think that it holds up quite the same way. I think there are a lot more treatments now that can push metastasis far, far out, including radiation and all the secondary hormonal therapies and all the wonderful things that you and your medical oncology colleagues have come up with. In my view, it's not as dire as before, but I'd love to hear your thoughts on that, and I'll head back to your second question.

Chuck Ryan:

I think it's a fair question. I do think about this though, and I do raise this with patients because I want to convey to them that even though they just have a rising PSA, that we have a potentially life-threatening relapse here. Obviously the timeline is very, very long. But the reason I ask you the radiation oncologist here, is there a point at which radiation is not beneficial because it's futile because of rapid doubling times because the patient has systemic disease and Dr. Ross is raising his hands. So I'll go to you, Ash.



Dr. Ashley Ross:

This is a really great point and this is the major difference in my mind between how medicine was practiced in the earlier time when these papers were written. There's another paper by Dr. Trock, we're going to talk about it in a second and then now, and it's a phase shift for the people on the call to think about and for them to tell other people facing prostate cancer. In the early 2000s for us as surgeons and as we were figuring it out, I don't think we were necessarily doing a great job. Because what we were doing was we were doing surgery and we're not integrating the multidisciplinary care with our radiation oncologist that we should be doing now. We were doing surgery and we were telling people, "Just watch your PSA. We'll use that to tell if you have metastasis or not."

We may not do radiation. Radiation can be harmful and that's by and large A, not true and can get people into trouble and certainly not true now where radiation has become much more precise, side effects are low. There was a paper written by Dr. Trock a little bit around the same time that showed that the people that benefit most from radiation therapy are the people with the shortest doubling times under six months, under three months. Those people benefit the most, and then the one caveat is, they benefit the most because their cancer is aggressive and it has metastatic potential, but you've got to get this radiation in when it's going to cure them in the pelvis. So yes, if you wait till like the PSA is one or two and they have a fast doubling time, you may not help them by local radiation.

Those are the people that Paul was saying earlier, you get the PET scan and they already have distance disease, but if you can get in the radiation while the PSA is low before it gets above 0.4 by some data from Stephenson and others, but certainly even at the 0.1, 0.2 range, that's the guy who has the most to gain, and my patients have to understand if they get the biochemical recurrence, 80% chance my radiation oncologist can give them that second opportunity towards full cure, I think, regardless of doubling time. It just tells the patients, "Be vigilant of your PSA when it's in the low levels. If it's doubling, pull the trigger when it's going from 0.1 to 0.2, not when it's going from one to two." And that would be my two cents in there.

Chuck Ryan:

Paul, your thoughts on that?

Dr. Paul Nguyen:

A hundred percent agree with both of Ash's cents there. I agree with Ash a lot. We think a lot alike, but I think that's really important. When I trained in the early 2000s, we were doing what Ash said and what you had been talking about, Chuck, that if somebody came into us with a rising PSA after prostatectomy, we try to sort out, who's got favorable enough disease that it's worth it for us to radiate and for whom is the disease just too aggressive and were not going to make a difference? And that Trock paper that Ash talked about turned that thinking on its head and made us realize that, "It's actually the patients with the more aggressive disease, it might benefit more the patients with the shorter doubling times." That's something that I try to drill into my residence's heads. That was a great paper that really completely changed our way of thinking about that.

Chuck Ryan:

Can I just jump in here? But yet the nomograms Stephenson paper that have been recited and redone, short doubling time is always a risk for failure of salvage radiation therapy. The question is not who has the... By looking at the whole population, I think what you're both kind of saying is that there is a window for cure there, but it's a window. I think Ash hit the nail on the head, basically said, "You've got

a rapid doubling time, but you've still got focal disease." And I think we've confounded that notion of the rapid doubling time with the distinction of focal versus systemic disease. As a medical oncologist, I think I try to consider myself sort of the skeptic or the advocate for the systemic approach because what kills people is systemic disease, spreads through the blood, spreads through the lymph nodes, goes to the bones, et cetera.

What you're saying is that the Stephenson papers and all those that say rapid doubling timing radiation is less likely to work is essentially saying that yes, but that's when you consider the whole spectrum of a rapidly rising PSA population, whereas there is a group in that window that can be cured, and how do we identify who they are?

Dr. Paul Nguyen:

I think all that you and your colleagues have done, Chuck, with systemic therapy, as your systemic therapy has gotten better, it's made the radiation more able to have an impact. As you're able to control the micrometastatic disease for these patients, it actually matters more that we're giving local radiation.

Chuck Ryan:

Let's get to that. But before we do that, bring us up to speed on the second part of my question and I shouldn't ask two-part questions. I know it's not fair, but the second part was, how do you use that data to know when to radiate, who to radiate, how far to go in the pelvis? Walk us through how you think about when you're going to apply radiation and then we'll talk about the hormone therapy.

Dr. Paul Nguyen:

Absolutely. In my ideal scenario, I would see patients after surgery when their PSA is risen to 0.1. As soon as it's gotten to 0.1, I would love to be seeing them and having a discussion at that point. In fact, for most patients with a PSA of 0.1, as long as they're reasonably healthy, I will go ahead and suggest that we start radiation and hormones. I actually don't get a chance for most of my patients to play with doubling times or observe doubling times because by the time we hit 0.1, I'm ready to go and I usually don't factor doubling time into my calculus.

We used to just treat the prostate bed, which is that area which is the anastomosis and the area behind the bladder. It is like a yay big area, around this big maybe 5x5 centimeters, 8x8 centimeters, something in that range, just around where the prostate used to be. What we have learned in the last three years from a nice study that came out at ASTRO is that there may be an advantage to treating the pelvis as well for some patients. There's a pretty strong evidence that it improves biochemical recurrence-free survival to include the pelvis and even a hint that there may be some benefit in metastasis, but it is not quite significant yet. And so this has changed a lot of our thinkings about treating the pelvis. I used to never treat the pelvis. I used to just treat the prostate bed and now I would say I treat the pelvic lymph nodes most of the time.

One of the factors that I would use to push me definitely towards treating the pelvic lymph nodes is the PSA level. If the PSA level is higher than 0.34, then in that study those patients definitely had a benefit to adding pelvic lymph node radiation. I've kind of taken it on to say, "Well, maybe patients with more aggressive disease would also benefit, maybe younger patients would also benefit." For me at this point, I'm trying to find a reason not to treat the pelvis because it's not that toxic to treat those pelvic lymph nodes. Yes, you get a little more diarrhea, but overall it's not that much more toxic long term, already in there and it could prevent a pelvic nodal failure if you've got microscopic disease in the nodes. And so



for most patients, I am treating because it's hard for me to discern who won't benefit from pelvic lymph node treatment now that we know that there is some benefit to it.

Chuck Ryan:

Can you give our listeners a sense of the difference in radiation dose when you do the radiation to the pelvis versus the prostate bed?

Dr. Paul Nguyen:

Sure. I think the easiest way to visualize it, I wish I had something like Ash did with the seminal vesicles or my ears. I don't have such a visual on my body ready to go yet. But if this area, maybe from my neck down to around here is sort of the prostate bed, adding the pelvic lymph nodes goes above my head. So the volume of your body that we're treating, it's probably three to four times as much the volume.

It's a lot of volume. However, we use lower doses in the pelvis. Whereas we treat the prostate bed down here where your prostate used to be, we might treat that to close to 70 Gy. We might only treat the pelvis to about 50 Gy. That's because the small bowel can't really tolerate that much radiation and because there's probably less disease up there in the pelvis, so we don't need to take it to as high a dose.

Chuck Ryan:

Okay. Go ahead.

Dr. Ashley Ross:

One point on that, what I'm usually telling my patients is kind of like Paul, I favor radiation to the pelvis and the prostate bed and I'm usually telling my patients the reasons not to do it. As Paul said, it's not dose and stuff like that. Don't worry about it. For you as a patient if you have very bad bowel symptoms, he was already mentioning this, lots of diarrhea or give inflammatory bowel disease, known Crohn's, known ulcerative colitis, these are things that you would be very leery about, do I have to radiate those areas or not? But if you don't, I think in most scenarios, you have normal bowel function. I think we've had really good results of radiation within the pelvis too, and I think it does prevent nodal recurrences. And the study Paul said was a great one.

Chuck Ryan:

Paul, should everybody get hormones? Who has a certain Gleason or a certain PSA, or what are you doing at Dana-Farber?

Dr. Paul Nguyen:

That's a two-hour conversation, Chuck, do we have two hours to talk about that?

Chuck Ryan:

I do.

Dr. Paul Nguyen:

I'll say it on the short and short, I'll say there is controversy out there. I think that there is very solid evidence that the hormones in many patients can improve outcomes. At Dana-Farber, I would say that

for most patients with sort of intermediate-ish risk disease, sort of like a Gleason, let's say 7 or early 8 with some extra cancer extension or something, we might give six months of hormones. For patients with very bad disease, so Gleason 9 and seminal vesicle invasion and a PSA of 1.5 and you're very young, you're 59 years old, we might even do two years of hormones like what was seen in the RADICALS-HD trial. The real controversy happens when your PSA is less than 0.7 because there is some data out there that suggests that hormones isn't important for those patients.

I, in general, tend to give hormones for those patients. The only patient that I don't give hormones to or recommend hormones to is somebody, let's say with a Gleason 7, T2 disease, meaning everything was confined to the prostate and they have a positive margin. In that scenario, I think it's pretty likely that whatever's there is just right where the surgeon cut out the prostate. And so probably the disease is right there, I can probably get away with not having the hormones.

But the nice thing about hormones is it can treat micrometastatic disease and it can help us better control disease. I do like it in most scenarios. There's a lot of nuance there. Another thing that we could do is as Ash's often mentioned is use a decipher test. For patients with a PSA less than 0.7, Felix Feng has nicely shown that those with a high decipher or intermediate decipher appear to have a benefit from the hormones, whereas perhaps those with low decipher don't. There's definitely a lot of nuance. I would say, in general, I tend to give at least six months of hormones, but I know that there's variation in how people think about that.

Chuck Ryan:

I agree. Just as Ash said that there's this window of curability, even when the PSA doubling time is really short, I would say that there may be a window of curability when there's a burden of systemic disease in the circulation, but it's very low and if it's very hormone sensitive that the addition of the hormone therapy may be able to control that. We don't know the answer to that question. In the world of radiation oncology, there's a generally accepted paradigm over the past 30 years that higher risk disease when you radiate giving hormones, helps the radiation.

It's as if the hormones were helping the radiation to deliver a dose of lethality to the tumor, whereas in actual fact, it could be that the hormone data has been generated over the years has been better earlier control of systemic therapy. The truth is probably somewhere in the middle of course, and we could debate that. Suffice to say, in the setting of salvage radiation, there really is not an accepted role for hormone therapies with an accepted duration. It's acceptable to use it in high risk and defensible. And I think a lot of us in academic centers are pretty quick to use hormones because of these considerations. But I don't know that we can say there's a textbook answer to this question.

Dr. Paul Nguyen:

I think that's fair.

Chuck Ryan:

Let's talk about a couple of other scenarios here. You mentioned the T2 patient with a positive margin at Gleason 7, and that stands out as sort of the best case scenario where you've got the positive surgical margin. So you literally know by reading that pathology report that there was tumor left behind. And you've got a situation where, as you said, it's likely that all of the cancer is there in the prostate bed. It's important I think to convey that to individuals. But even within that setting, you have a spectrum of high risk decipher, high risk other factors that might make radiation therapy less available. And so Ash, just a brief digression on this idea of prognostic versus predictive tests because I think for patients it's very

confusing. They may have a high risk decipher. What does that mean about their risk overall, and what does that mean about the likelihood of radiation benefiting them?

Dr. Ashley Ross:

I think, just so we go to the distinction, so we sometimes will, usually scientifically or when we're discussing as colleagues, will think about prognostic and predictive risk. Prognostic is higher risk your disease is going to do worse just overall. Predictive is usually saying like, "If we give a specific therapy, will this test the thing that tell us that you're going to respond better to that specific therapy versus another therapy?" And there's a lot of overlap. We'll see things like Dr. Nguyen was mentioning, one of the STAMPEDE arms, there's like Arm G of STAMPEDE where for guys with at the highest risk, if they had higher decipher, they sometimes would be doing better if you gave them multimodal systemic therapy with the radiation versus if they had a lower risk. I think that for the patients, it's not important to understand these nuances.

In some cases there are some tests that where it's really predictive, but even those get muddied like you have a BRCA2 mutation and you're going to give a PARP inhibitor for that BRCA2 mutation, you respond better, it's predictive of response. I don't think it's that important for the patients to understand it as much as it is for the decipher for example, being high, we were talking about. It means your disease is going to do worse and it so happens that high risk decipher patients in the context that we're talking about getting salvage radiation seem to have more bang for their buck with the hormonal therapy. Now does that mean the high decipher is predictive of response to hormonal therapy? Probably not. It's more of a prognostic marker in saying that those guys are going to have worse outcomes. Hormonal therapy tends to add to radiation, whether it's boosting the efficacy of the radiation or controlling the micrometastatic disease.

For you as the patient, you just want to know what you should do to make your outcomes better. And decipher is more of a prognostic test, but there may be baked into that, some predictive components. And then there's something even further from that we'll call the decipher grid, which they're looking at specific signatures. But right now for you, the patient, don't worry too much about predictive or prognostic in this setting until we get better data on truly precision driven individualized regimen. Right now we're talking about using radiation and hormonal therapy, which are kind of like, I don't want to say they're hammers, but they're more patient agnostic. In the hormone sensitive setting for prostate cancer, almost all disease is going to be responsive to hormonal therapy.

And in the hormone sensitive setting, almost all the disease is going to be somewhat radiation responsive as well when we're talking about these low PSA. And so you're really thinking about, "Is my disease risky enough to treat or not? And if I'm treating it, how much do I want to think about a micrometastatic component or do I want to boost it with the radiation?" And those are kind of a circuitous answer and I'm sorry about that, Chuck, but really the patient should be thinking, "Is my disease risky enough to treat, and how much should I put the hammer down on that treatment," more than like, "Am I going to be radiation responsive or not, or hormonal responsive or not?"

Chuck Ryan:

It's a really important set of issues and it highlights an area that we need to continue to research because there is confusion on this. We are now integrating a lot of biological knowledge into this question on when and whether to use radiation and other therapies. Thank you for that clarification.