

Chuck Ryan:

I am Chuck Ryan. I am the president and CEO of the Prostate Cancer Foundation and your host. So tonight I'm thrilled to have two guests who are joining me. First I'm delighted to introduce Dr. Ashley Ross, MD, PhD from Northwestern. And 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. Ash, Dr. Ross, thank you so much for joining us.

Dr. Ashley Ross:

Thanks so much for having me.

Chuck Ryan:

And 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 at 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 personalizing treatment for men with localized prostate cancer using all of the tools that we can today, which is genomics, clinical factors, et cetera, et cetera. He's also got a deep expertise in 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:

All right, I want to do a couple things. I want to talk about what we do if you've had surgery and you've had radiation and then your PSA's rising. But before I get to that, we haven't even covered the other side of the coin, which is patients who never have surgery, they opt for radiation at the outset and then they have a rising PSA after radiation. So Ash, I'm going to just ask you this one first. Should these patients go and have their prostates removed after radiation has failed to cure their cancer?

Dr. Ashley Ross:

Yeah, so it's a great question and there is plan Bs after radiation. So essentially your PSA will drop after radiation. But remember, radiation's going to kill prostate cancer more than it's going to kill non-cancerous benign tissue. And so your PSA will not always go to zero and that's okay. And so what they're looking for as a patient after radiation is some sign that there may be residual disease. And just to talk about this for a second, that's either going to be accepted would be a PSA that's low and does not rise to two points above the lowest point. So if your PSA at the lowest point was 0.01, then we don't want it to go to two. And the other thing that we sometimes will use for some patients, although it's more debatable 'cause there'd be inflammation and stuff like that, is consecutive rises, like three consecutive rises, in the PSA, might give us some concern.

At that point, you as the patient want to know the same things we wanted to know after surgery, but we have a little bit more issue there. And that is, what's making that PSA? Is it disease that is persistent or recurrent in the prostate? Is it disease that's elsewhere in the body? And so the guy that has a PSA of say, two after radiation and the lowest they went is like 0.01 or less than 0.1, we're going to do a biopsy of their prostate to figure out is there recurrent disease in the prostate. We're going to do a PET PSMA

scan or some other PET scan to look throughout their prostates, throughout their body and see where is it coming from.

Now say the disease is just in the prostate. That's your question, Chuck, of like, "Should we remove the prostate now or should we do some other therapy?" The issue is that radiation therapy, the benefit of radiation upfront for a lot of patients is we don't rearrange the anatomy when you give them primary radiation. So they don't have to go through the continent's recovery when you give them radiation upfront.

The negative is it sort of freezes things in time a little bit because it affects the small blood vessels that deal with the tissue around the prostate. And it makes it so that if now you're going to do a reconstructive surgery, remove the prostate, reconstructing, the chance of that healing well and getting good continents, which is leakage of urine is lower. As opposed to people going to surgery upfront, we tell them one to 5% might be incontinent long term. After radiation then surgery and removal, it might be up to half of the men will have kind of bothersome incontinence.

But there's other plan Bs. I mean this is really, even though a lot of ablative therapies like HIFU, cryotherapy, et cetera are being looked at for focal therapy upfront, their real wheelhouse, particularly cryoablation, which was FDA-approved here is after radiation failures. If their disease is only in the prostate, yes, you can remove the prostate, but that will cause some incontinence there're high amounts, et cetera, et cetera.

But you can also do a of therapy to the prostate like cryoablation and other methods that can attack the cancer in the prostate. And a lot of times if you jumped on it early PSA is now less than four in this salvage after radiation setting, those men will have very good outcomes. And about 70% of them can go into deep remissions. And so we can expand on this, but that's kind of the idea. I think that therapy to the prostate, not necessarily removal is doable in the postradiation setting. And just like with surgery, we want to jump on it early when we have a chance to attack it in the prostate.

Chuck Ryan:

There aren't a lot of urologists out there doing salvage radical prostatectomies for the very reasons you cited.

Dr. Ashley Ross:

Exactly. It is a doable procedure. I do them, I sort of hate doing them because the stakes are really high. If there's an injury, things will not heal. Rectal injury would be the worst. They might require colostomy and because we know that our urinary outcomes are not going to be as good. But every once in a while I think it's the treatment of choice. And that is for, there's men that have, even though their radiation oncologists often told them, "Do not do radiation," they were below 60 when they had their radiation and they're still young with 20 years to go. And we have to think about what we're going to do to salvage them so they don't have to be on hormonal therapy for that long period.

And secondarily, they have disease that's in the seminal vessel. So this is tough, but again, my bunny ears, when Paul's radiating me the first time, he's radiating my head where it was and maybe he's radiating the lymph nodes in some cases off in my head. My bunny ears here actually are beneath the bladder and they're in a somewhat hard spot to really treat hard without giving a lot of toxicity. Nowadays, they do a better job 'cause they can really sculpt. But particularly in the past and particularly with, I think with brachytherapy, it's a hard area to radiate. So young guys with disease in the seminal vesicles on recurrence with disease that's periurethral like right next to urinary tract where ablative therapies are going to cause strictures and other things. Those are my wheelhouse for salvage

prostatectomy. And I only may do a handful of those a year where I might do one or 200 prostatectomies a year. So it's [inaudible 00:06:55]-

Chuck Ryan:

Yeah. So Paul your thoughts? Are your thoughts on as a radiation oncologist addressing the issue of relapse after radiation? How do you think through it?

Dr. Paul Nguyen:

Yeah, same way as Ash thinks about it. If there's going to be some patients where it's really all in the prostate, and if it is, then we have to think about salvage surgery as Ash talked about or we can sometimes do salvage radiation where we put catheters inside the prostate and use high dose rate brachytherapy. There's probably the longest and best track record with that in terms of radiation salvage options. Or, we look to our colleagues who do HIFU cryo or other local ablative therapies.

And then there's the thought about what do you do for disease where, and actually let me just say for the most part in the United States, even though we have talked about very aggressive salvage local therapies, for the most part, if you look at the CRM Medicare database, which is how most patients are treated, something like 90% of patients with local recurrences don't get salvage local therapy. Most patients get treated with hormones or observation, which I'm sure you can talk about much better, Chuck.

But then there's the other category of disease where it comes back after radiation, but it's not in the prostate, it's someplace else. And that's where we're going to have to look for it with a PSMA PET, and maybe we can do focal local radiation if it's just in the pelvis or in a bone and give some hormones along with that which-

Chuck Ryan:

Yeah, I'm going to take us there next, which is this idea of even if you've had surgery or radiation or you've had surgery, then radiation and you've exhausted the local treatments to the prostate, there's still a potential curability window I think, which is people with oligometastatic disease, which is one or two, maybe three or four isolated metastases that may be the major site for the recurrent PSA and those can be treated with focal therapy. And so as you think about salvage radiation therapy, I think your world has expanded, Paul, a little bit into doing things like metastasis-directed therapy and this could be a topic for another day, but your current thoughts on that approach and then I will discuss hormones a little bit.

Dr. Paul Nguyen:

Yeah, I mean, right. My world used to be from here to here, the prostate bed and the pelvis, and now it's all over. Thanks to the NICE studies suggesting that if somebody just has one or two or three, maybe even four metastases, that doing high dose radiation directed just at those metastases that might be in the bone or in the lymph node can actually make people live longer. We have one study called the COMET study that suggests that some people think that study is a little incomplete and we need to follow it on with a bigger phase three trial. But that I think has really changed our paradigm for a lot of patients where we used to think that if you got metastatic disease, then there's no role for radiation. Now all of a sudden there is some evidence that really treating it to high dose can make a difference. But of course when we do that to really get the long-term benefit, I also think we need systemic therapy, the things that you and your colleagues offer, Chuck.

Chuck Ryan:

Right but I think a closing 10 minutes or so, this notion that you can cure metastatic cancer or metastatic prostate cancer is kind of a new way of thinking because the old way of thinking was once it had escaped the prostate, it's a systemic disease and needs lifelong systemic therapy, et cetera, et cetera. And we're seeing people now, and I have patients back from my UCSF practice, for example, a person with I remember I followed him for 10 years after there had been metastasis to his vertebral to a vertebral met and was appeared to be cured from that isolated metastasis. So Ash, you had a comment?

Dr. Ashley Ross:

Before we move on to this complex part, just again for the audience, it's good to think about the number four or some iteration of point of four. So if you had surgery, just surgery and somehow you've made it through and your PSA is now 0.4 or above and nobody has talked to you about salvage radiation, there's a problem. You need to talk to someone about salvage radiation. If you've had radiation, whether it be brachytherapy, external beam radiation or something like that, and your number of your PSA has made it to four and no one's talked to you about salvage therapies locally that could cure you after radiation, that's a problem. You need to talk to somebody. And like Paul mentioned, after radiation, we often tell people, "Don't do surgery. You're going to have lots of side effects," and we use hormonal therapy all things, but as Dr. Nguyen, Paul, mentioned, high dose brachytherapy, cryoablation, these things don't rearrange the anatomy. And you have about 70% of the people can be cured and never have to go on to any more therapy if you treat them early enough.

So your number at the audience, if you've had a radiation be watching your PSA. If it gets to four and nobody's evaluated you with a PET scan, with a biopsy or anything, that's an issue. If you had a surgery and you're 0.4 and no one's evaluated you, that's an issue. I'm not saying that you shouldn't have evaluation even earlier. I'm just saying those are the hard lines that should set off your alarms. And before we get to something complicated, Chuck, which I know we're going to do in the last 10 minutes, I just wanted to make sure everyone knew that.

Chuck Ryan:

That's a great clarification. And I think that it reflects some of the challenges we see as we look at implementation of new therapies and even old therapies in the United States. I think, Paul, you mentioned it, a pretty small proportion of patients who are getting salvage radiation who could and could potentially be cured. And so we're missing the opportunity in this country to cure individuals and we're putting them on therapies. And this is my segue to talk a little bit about hormone therapy. If we're taking somebody with three or four metastases and putting them on lifelong hormonal therapy, that person is probably, A, potentially missing an opportunity to be cured. And B, they're getting potentially unnecessarily long hormone therapy. So with that, I just would close and say that as a medical oncologist, as I started out the top of the hour, I said that a common referral for me is somebody who had surgery then had radiation, PSA is still rising, and now what do we do?

So the first thing we do is, as Paul said, we do a PSMA PET when we can do it. And we try to isolate whether there are a couple of focal metastatic lesions that we can treat with radiation therapy. One area that's problematic is we see a lot of bladder neck recurrence in patients who've had, it's a not uncommon thing. People have had surgery, they've had radiation, and they have a PSMA PET, and the only place we see disease is in the bladder neck. Well, we can't radiate that again. And on the one hand, on the other hand, it's a pretty small burden of disease. But I will point out that we've made a lot of progress over the past couple of decades with the integration of systemic therapy into earlier and earlier disease states.

So for example, it was a long-accepted standard that men with metastatic disease would receive ADT alone, and then when their disease worsened, we would intensify with chemotherapy or additional hormone therapies such as abiraterone or enzalutamide. Well, we could sort of prove that doing that upfront is better for patients with overt metastatic disease. So what that means is that if you have true metastatic disease at the time of diagnosis, not three but maybe 15 metastases, we know for example, that adding abiraterone or darolutamide or docetaxel adds and improved survival and delays complications.

So we've tested that same paradigm in the patients who don't have overt metastatic disease and who are faced with a rising PSA after radiation and surgery. And we're beginning to see hints that this paradigm exists even in this setting of a rising PSA only. And there was recently a study presented called the PRESTO trial, which looked at three arms, but it was one year of ADT, one year of ADT plus apalutamide, one year of ADT plus apalutamide and abiraterone. So it was single double or triple therapy. And it looks like double and triple therapy are better than single therapy. And we don't know if double or triple therapy are different from one another, they probably aren't.

But the idea of the intensification is important. And the idea that I try to get across to my patients is that intensification of hormonal therapy can allow us to shorten the duration. So gone are the days of taking a man with a rising PSA and saying, "Sorry, you need to be on loop," or, "You need to be on ADT for the rest of your life." Nobody should ever hear that anymore. Okay, because a rising PSA is a potentially curable situation with all of the approaches that we talked about before. But even when it's not, we typically are doing intermittent hormonal therapy for reasons that we really don't have time to go into because they're running out of time. But that'll be a topic for another day.

And what I would say is ask your doctors about hormone therapy, intermittent, I typically do a year at a time. For patients with a rapidly rising PSA, I'll do intensification usually with abiraterone or a similar drug during that time period. So we manage to really fill an hour with a really complicated, but really kind of a very common issue that many men face, as I've said, 30 to 50,000 Americans every year being diagnosed with this after undergoing treatment with curative intent. So I'm going to let the two of you close it with a couple of final words. Paul, I'm going to go to you first.

Dr. Paul Nguyen:

Yeah, I just appreciate the opportunity to be here. I see there're over 800 people online, so I apologize that I know there are a lot of questions, 138 questions in the chat. I'm sorry we haven't been able to answer all of them, but hopefully this information was useful and it's online. And I think the key thing is speak with your doctors. Get in early if your PSA is rising, and talk about it and get a multidisciplinary discussion like we've been having here.

Chuck Ryan:

And advocate for yourself. Ash?

Dr. Ashley Ross:

Yeah, thanks. Thank you for having me. And I agree with Paul entirely. The thing to realize is in prostate cancer, instead of doing everything in parallel, which means everything at the same time in order to save you from some morbidities, and because we have some good tools with the PSA, we are going to often layer therapy. And you have multiple opportunities to get cured when your disease is in the pelvis and then contained when it's outside the pelvis may be remission.

So what you want to do is to have your initial therapeutic approach, follow yourself carefully. Look at that PSA. It's a great indicator of what's going on, and then intervene early with a second opportunity to cure if you see some warning signs, and that's a PSA rising after surgery, PSA rising after radiation. Your hard lines are 0.4 and four after surgery, after radiation. But your soft lines after surgery might be values of 0.03 to 0.1, and then certainly at 0.1 to 0.4 and after radiation, it might be values as low as two. And just get in and talk to your oncologist, figure out what, reassess your disease, and then look for that second opportunity for cure or an opportunity for some containment, as you were mentioning, Chuck, with systemic therapy.

Chuck Ryan:

And for more information, go to pcf.org, get our patient guide. Also go to urotoday.com with a lot of meeting coverage and late breaking news and a lot of deep thoughts from many clinicians from all over the world talking about what they do and why they do it, and how the data drive what they do. Also, look forward to next month's webinar, and we will get some announcements out about that. And thank you to Dr. Nguyen from Dana-Farber, radiation oncologist and Dr. Ash Ross from Northwestern, urologist, delightful talking to you. And good night, everybody.