When Your PSA is Rising After Treatment

Becky Campbell: Good afternoon. Good evening, everyone, and thank you for joining us tonight. In just a few moments I'm going to introduce our host, Dr. Phil Koo, but I'm just going to go over a few housekeeping items tonight. We really appreciate your joining. It's because of your interest and your support that we produce these webinars. So we thank you very much for taking time out of your day to join us.

So the webinar is being recorded, and you'll receive an email with the link to view it in about a week.

You can type questions using the Q&A icon at the bottom of your screen. We'll have some time at the end for questions. Please make sure not to include personal medical information, and please do consult your healthcare provider for personal medical advice related to your situation.

We have a number of other resources at our website, pcf.org, if you have other questions about issues related to prostate cancer that we don't cover this evening.

I'd like to thank Pfizer for their support of this program, and also note that all views expressed tonight represent those of the speakers.

Here's a brief overview of our agenda. We're going to speak generally about rising PSA and how patients are monitored after initial treatment for localized prostate cancer.

And it's going to be divided into two sections this evening. First, speaking about the process of monitoring treatment, evaluation after surgery, and the second part for patients who have been initially treated with radiation therapy. So we encourage you actually to stay tuned for the whole webinar, as there may be some overlap between those two topics, and then we'll wrap up with some Q&A about 10 to 15 minutes towards the end.

In case you're not familiar with the Prostate Cancer Foundation, I'll just provide a brief overview. So our core mission is to improve and extend the lives of patients with prostate cancer through research. We do this through funding projects around the world, about 2,200 and counting. And many of the therapies used today, particularly those to treat advanced prostate cancer were actually developed with early stage research funding from PCF.

And we're–other types of research that we're funding around more precise diagnosis helping providers to, and patients to select the most–therapy that's most appropriate for them, whether through studying genetics, imaging other types of biomarkers to really help patients choose the best therapy.

We also aim to empower people with knowledge to help guide their care in discussions with their healthcare provider. So you can go to pcf.org, find patient guides, other past recorded webinars.

I'd like to call your attention to two upcoming webinars. We'd like to invite you to join us next Friday. Dr. Koo will be in conversation with urologic oncologist, Dr. Zach Klaassen. They're going to be discussing the latest updates from two recent conferences, both in localized and advanced prostate cancer. And I'll be putting the link to register in the chat as we move forward.

Then join us again at the end of May. We'll be diving down into hormone therapy. We'll touch on that briefly tonight, but join us at the end of May to really get into the different types of hormone therapy when it's used, how it's used, side effects, etc.

And I'd also like to encourage you to go to Prostate Cancer Patient Voices [prostatecancerpatientvoices.com]. That's our companion website, where patients and caregivers really tell their stories in their own words.

Our website is now launched–a new pcf.org just launched last week, so it'll look a little different if you go to the website now, and we're endeavoring to fix any broken links. Please be patient if you find something that you're not sure about. We are actively working to just make sure that it's the most easily–easy access to all this type of information that you're interested in, so very excited to launch our new website.

I'd like to introduce our panelists and thank them for joining us tonight to share this very important information. Dr. Leslie Ballas is a professor of radiation oncology at Cedars Sinai Medical Center. She specializes in the treatment of GU cancers and as well as an expert in hematologic malignancies.

She has–she's a co-author in more than 100 peer reviewed publications. She was recently honored as a Fellow at the American Society for Radiation Oncology, and she is also the editor–an editor of our Patient Guide to Localize Prostate Cancer. So thank you, Dr. Ballas.

And I'd also like to introduce Dr. Jason Hafron. He is Chief Medical Officer at the Michigan Institute of Urology. He's also a professor at the William Beaumont School of Medicine. He's published many, many peer reviewed journal articles, presented his work at many prestigious conferences, and is also an editorial board member at a number of publications.

So without further ado, I'd like to welcome Dr. Philip Koo. He is PCF’s new Chief Medical Officer who is going to be leading the discussion today. Thank you so much for your attendance, everyone.

Dr. Phillip Koo: Great. Thank you all, and thank you, Becky, for the introduction. And congratulations to you and so many members of the team that put in so much time and effort in revamping that website. And for the people on the line, I encourage you to go check out the website. There's so much great information beyond what we'll talk about today. So today, we're talking about biochemical recurrence. We're talking about the rise in PSA after you've received definitive treatment.

So we're not talking about PSA persistence. We're not talking about biochemical recurrence down the road after multiple lines of therapy. So we're really going to drill down in this one area, just because there's so much to talk about. And we know that this is one of those areas that patients get very nervous about.

And to speak about this topic again, we have two amazing speakers, Doctors Ballas and Hafron, who are very active, not only in the clinical trial piece, but also very passionate and fierce advocates for patient care, which is what we all want and need. So thank you guys for being here.

Dr. Jason Hafron: It's my pleasure.

Dr. Leslie Ballas: Thank you for inviting us.

Dr. Jason Hafron: Okay.

Dr. Phillip Koo: All right. So let's just sort of start with a high level view. You know. You get your prostatectomy. You get your definitive radiation, you know, you hope you're cured. But unfortunately things occur. What advice in general do you have for patients just to sort of manage the emotional roller coaster you might be going through? So I'll start with you, Leslie.

Dr. Leslie Ballas: Yeah. So again, I'm a radiation oncologist. So I'm just going to speak initially to what happens, you know, after definitive radiation for prostate cancer. And you know, we always counsel our patients that–not to hang their hat on any one PSA value. After radiation, your prostate is still in your body, and so your PSA can fluctuate a little bit.

That can be challenging for patients, because maybe it goes up a little bit and then up a little bit more, but then comes down by the third visit, and so we are always, you know, just making sure that patients have regular follow up with us so that we can help put PSA values in context.

Similarly, with radiation, some patients get hormone therapy in addition to radiation. And hormone therapy can drive down the PSA. So there's always that reminder to patients that when their hormone therapy is done and their testosterone normalizes, their PSA may also rise in accordance with that, and that we try to put that into perspective.

So I think that just following the numbers, especially after definitive radiation, isn't the whole story, and that putting it into context based on your testosterone level, and/or what definitive therapy you had is really important.

Dr. Phillip Koo: I think that's great advice. So when you go into MyChart, you check your own labs. You know it's important to look at the labs, important to know your medical record, but make sure you speak with your physician and your team before you get too nervous. So how about you, Jason?

Dr. Jason Hafron: Yeah, I think, I agree with a lot what Leslie said. I think, you know, PSA is “Prostate Specific Antigen,” but what we commonly refer to as “Patient Specific Anxiety,” and I think patients get very wrapped up in their PSAs, and can really keep them up at night and lead to a lot of sleepless nights. I think what we have to know about BCR [biochemical recurrence] is that it's very common whether you've had surgery or whether you've had radiation. The recurrence rate in 10 years can be, depending on the initial grade of your cancer, from 20% to 50%.

So if you do see a rise in your PSA, and there's some nuances we'll get to tonight about radiation versus surgery, and the rates and stuff, but I think what's key is that just because you developed a biochemical recurrence, it's not the “end all be all.” Okay. It's not a death sentence. There are a variety of different ways to evaluate it. It's not truly clinical failure per se.

It just means that you may or may not need additional therapy, and we'll talk about it. You may or may not develop metastatic disease or spread of your cancer. So I think what I try to do in the clinic, when I see these–my patients, which we unfortunately see quite often, is to reassure the

patient that this is not a death sentence. This is not clinical failure, and we'll get to it tonight, but there's a lot of nuances that we'll see. It's not as bad as it appears after you fail the initial line of therapy.

Dr. Phillip Koo: All right. That's a great message. And I agree. I think we do have many more tools available, and we know more today than we did five, ten years ago to manage these patients better. So, good.

So just to level set. Jason, you know, I'll ask you this.
There are different types of PSA tests. Can you walk us through sort of the standard, the ultrasensitive? What do they all mean? What should we be getting?

Dr. Jason Hafron: Yeah. So there's a variety of different immunoassays that each of the hospitals or your offices will use. I don't think we need to go into the specifics of that, I think what's key is that you get your PSA at the same place. Because the assays can vary if you're going from one health system to another. And, I think, whatever that–whatever tool that they use or assay they use, just stay consistent.

As far as the ultrasensitive PSA, ultrasensitive PSA was big like 20 years ago, and we used to like, just, you know, go nuts. And looking at these micro-rises to the thousands of a point and and really drive people crazy, and drive the urologist crazy. We've kind of gotten away from it. I think, where we've landed today is that, you know, what we… true failure is 0.2 nanograms per deciliter. But where we get worried is when that PSA starts to creep above 0.1.

So anything below 0.1 kind of is to me noise. And I'm curious what Leslie thinks. But once you start creeping above that 0.1 to the 0.2 range, whether it's, you know, whatever assay you use. That's when, you know, we got to kind of get get focused and start looking at this critically.

Dr. Leslie Ballas: Yeah, I agree with Jason. The only thing I would say is that–and we'll obviously get into this. But when we talk about the point at which you want to trigger post-operative radiation, some of the best data would say that you'd trigger it at a PSA of 0.1 or higher, or if there were three consecutive rises.

So if you don't have an ultrasensitive PSA, if you're using a lab that only starts their PSA detection at 0.1, you may just not catch those three consecutive rises. And so that would be the only time that in my practice I would care about an ultrasensitive PSA.

Dr. Phillip Koo: Alright. Good. You know, these are all great points. I think the one key takeaway, which I think is wonderful and good for all of us to hear again is, make sure you go to the same lab for all the tests. So that was great.

So we're going to start off by talking about the patient who's had surgery. They've had definitive….They've had their prostate removed surgically. And that's, you know, a procedure that you would do, Jason. How often are you following them and getting PSAs?

Dr. Jason Hafron: In my practice. I check the first PSA within six weeks of the surgery, because I want to make sure that that PSA is zeroed. After the prostate is removed, the PSA should be essentially 0, depending on the lab–you know, we can get–but it's less than 0.1.

And then after that, for the first year, I try to check a PSA every three months for year one. Year two and three I check a PSA every six months, and then annually thereafter, and I follow patients for 15 years, and we'll check a PSA either myself or have them checked with their primary care doctor.

Dr. Phillip Koo: Alright. So that's great. So you're following these patients closely. There's a very set schedule, and the schedules might vary, you know, based on on the physicians, but in general you need to be–make sure you're being followed closely. At what point are you saying, “Alright. This patient has biochemical recurrence.”?

Dr. Jason Hafron: So like, I just said, when that PSA starts to–start to go above that 0.1, or you start to see any movement on that PSA, that's significant. Because that is raising awareness that something might be coming back.

And I think, and we can talk a little bit about the data. But what's clear with–in a biochemical recurrence, after surgery, is the faster that you can get them to radiation–adjuvant radiation, the better they will do. So we don't like to wait until that PSA starts to climb too high. We want to treat it very early, so that will lead to the best response. The earlier….

Dr. Phillip Koo: We're gonna talk about–alright. Thank you. We're gonna talk about that intervention early. And we're gonna save it for a little bit later, because I want to make sure we covered it completely. So you know, we're following PSA. We sort of define what biochemical recurrence looks like after a prostatectomy.

Does PSA doubling time–how do you sort of use that as a tool when you're following these patients?

Dr. Jason Hafron: PSA doubling time is a very, very important mathematical equation, and I'm just going to pause here because I think it's really critical that the audience and the patients understand it.

Basically, it's a mathematical equation that will predict likelihood of a future event, or in this scenario, could be metastatic or spread of the cancer. And what it is is a mathematical equation in months. So we calculate in months, the likelihood, or in months, how quickly your PSA has doubled over that period of months.

So it's a very important predictor when looking at these patients, to determine how aggressive this recurrence is. And there's a wide range of these recurrences, and we can talk about that, too, is some need to be treated and some can be followed, and a lot of it is based on the PSA doubling time. So I don't know what Leslie thinks, but to me, a PSA doubling time after a primary failure is very predictive and an important number to know when treating these patients.

Dr. Phillip Koo: Alright good. So you know, I think it's–I think that's great. I think it's one of those extra tools that we have just to sort of understand, you know, how things might go for that patient, and that'll guide some of our treatment decisions. So okay, this patient now who's had a prostatectomy. Their PSA comes to the 0.1 or goes above it. When is your sort of trigger with regards to getting additional imaging? So, when would you get a PSMA PET? When would you get an MRI?

Dr. Jason Hafron: Yeah, I mean, it's a little bit controversial today, but I have–I think PSMA PET is a disruptive technology that has a major impact on how we manage this disease. So I try to get it as early as possible, as long as the payor will cover it. But I do tell the patient, if we're checking PSMA PETs at this early level, it's rarely positive.

But occasionally, we will get positive results that can have a significant impact on how Leslie would treat this patient or how we would manage this patient. So I try–honestly, and, Phil, you're an expert on PSMA PET, but I try to PET as early and as often as I can to help manage these patients.

Dr. Phillip Koo: Yeah, I agree. I agree with you on that as well. Leslie, did you have any comments here?

Dr. Leslie Ballas: We typically don't get a PSMA PET until the PSA has hit 0.2. The sensitivity of PSMA PET, and Phil, obviously correct me if my numbers aren't right, but at 0.2 is somewhere in like the 35%, 40% range. And so therefore, you know, the chance of it be–I mean, I think it's important to understand, like, the chance of it being positive is so much less than the chance of it being negative.

I think Jason's 100% right, if it does happen to be positive that can be helpful. But we really want to give messages to our patients that when we treat for rise in PSA, we're treating because of the PSA. The PSMA, the PET scan does not need to be positive to get post-operative radiation. And I think that there has become some confusion that if you get a PSMA PET and it's negative, that you should wait until it's positive to get radiation, and I couldn't disagree with that statement more.

And so we've been able to hold off until about 0.2 with most of our patients, which is–and many of our patients, in fairness…We are pretty good about sticking to the data, showing that the benefit of radiation can wait until the PSA hits 0.1 or higher or three consecutive rises from the UK. And so there are many patients who don't get PETs before they get post-operative radiation.

Dr. Phillip Koo: Sure. So you know, I agree with all the comments. It's a very tricky topic right now, when you get it, I think in general, there is a lot of power in having a negative PSMA PET result, which provides a lot of reassurance that the disease is just local, and I think, as we talk about sort of how we salvage or how we sort of treat patients earlier, you know, I think this comes into the discussion.

So going back to that patient with biochemical recurrence. Do you routinely get an MRI in these types of patients?

Dr. Jason Hafron: I do. And I do it because I know our rad-oncs like it if we're gonna consider salvage therapy. So I would defer to Leslie, you know, in that setting, but usually they're the ones that are requesting it. So I will order the PET, order the MRI, and refer them to–for a second opinion with the radiation oncologist.

Dr. Phillip Koo: Great.

Dr. Leslie Ballas: If we're waiting to the point where we're going to get PSMA PET at 0.2, we're not typically also getting an MRI at that point, because PSMA PET has been shown to be a

more sensitive technology, and so we are typically not getting MRI routinely in these patients although, I think that's a practice pattern variation between radiation oncologists.

Dr. Phillip Koo: Yeah. And I think this is a good take home message, for you know, a lot–all the patients on the line that the practice patterns are very–can be different. And you know, cancer is very complicated. And that's why it's important to have multiple different specialties at the table and having discussions, and I know Jason, Leslie, I'll speak on behalf of them as well. They have a team behind them, and they have multiple different people who they'll talk to all the time. They're texting all day long, or calling, to sort of come up with the best plan. So, Jason?

Dr. Jason Hafron: Yeah, but I think the key, though, is earlier is better. I mean, I think not–you don't want to wait until the PSA gets high. All the data that Leslie touched on is patients do better when that PSA is in that 0.2-ish or around that 0.2. You know, I'm going to be broad here, but earlier is better. And I think Leslie's point is pretty valid, too, and it's a confusing issue with patients. So patient has a biochemical recurrence, we check a PET, we check imaging, and we don't see any cancer. But here I am telling the patient, “you know, your PSA has risen, and you're going to need radiation.”

What am I treating? Like, if you can't see it on the PET, what am I actually doing? Why do I need that? And that really gets a lot of patients stuck on–what if you can't see it on the PET scan, or you can't see it on the MRI–whatever imaging you're using, What are we doing? Why are we doing this?

And I think you know, and I'll defer to Leslie. But I think what we have is solid data that supports in those situations, if we give them early radiation, the patient we can, you know, we can salvage them and get their PSA back to zero.

The other issue–and Phil, you know this–is that the PET scans aren't perfect. They can't see disease less than 5 millimeters. So there can be micrometastatic disease that, statistically, is probably in the pelvis, where the prostate was, or in the lymph nodes surrounding the pelvis.

Dr. Phillip Koo: Yeah, I agree. You know, PET/CT, MRs, are not perfect. We miss microscopic levels of disease because they're microscopic.

So, good. Alright. So when you're counseling this patient, they have biochemical recurrence. Does genetic testing ever come into play? Are there other things that sort of go into risk stratifying or understanding how risk–where they might be in terms of recurrence, like a more aggressive recurrence, a lower aggressive recurrence?

Dr. Jason Hafron: Yeah, I mean, genetic testing should always be done. If there's a strong family history, a history of Lynch syndrome, if they initially have high risk disease. But it's really, if they're not truly metastatic, we wouldn't routinely do genetic testing. And also, I think, where we've used genomic classifiers, there are molecular tests that will show based on the–a sample of the prostatectomy, of what we removed, whether there is benefit to using hormones with the radiation. So we do use some of that to guide some therapy, but it's not like a–it's important, but I wouldn't say it's critical. I think it's a part of the process, and it will kinda, you know, stratify patients a little bit more on how significant or how aggressive their disease is. But it's not a critical step to moving forward with treatment.

Dr. Leslie Ballas: I agree with Jason. I think it's really important for patients to understand the difference between genetic testing and genomic testing. So genetic testing is like, “I have hazel eyes because my dad has hazel eyes.”

Things that get passed down from generations for the most part, whereas genomic testing is like Jason described, taking your tumor that's already been taken out of your body, a sample of it from the pathology, lab sending it for analysis of different mutations, alterations, things within your tumor that could make it more high risk, and that can help direct whether or not hormone therapy would be needed in addition to radiation. But I commonly find patients get a lot of confusion around sort of those 2 things, and as Jason mentioned, there are patients who have true genetic connections with their prostate cancer. But we haven't routinely checked genetic testing after a prostatectomy.

Dr. Phillip Koo: Alright. Great, that's really helpful. I think there's a role for genetic testing, so your family lineage. And then there's a role for the testing of your specific tumor, which is good because you know, the center should have hold on to the sample, and they can send that out if needed. And again, these are just more data points to help guide how we go to your next part of treatment, which the goals of care would be, you know, obviously prevent metastases or treat metastases. We've talked a lot about this early intervention and salvage.

So what are some of our salvage options now in this post-prostatectomy patient who has biochemical recurrence? And I'll start with you, Leslie.

Dr. Leslie Ballas: So if a patient has a lifespan that is greater than 5 years, we would say that the NCCN, or the National Cancer Care Network guidelines, would indicate that radiotherapy to the prostate bed–the area where the prostate used to sit, plus or minus, including the pelvic lymph nodes depending on the specifics of a patient's situation, would be the next level of care for patients, as long as they had no evidence of metastases. That can be done in combination with hormone therapy. And that's again where we sort of would maybe use the genomic testing.

Another option would be potentially for patients, maybe hormone therapy alone, if they had certain…either metastatic disease, or if they had lymph nodes involved at the time of surgery, and for whatever reason, were not a radiation candidate. And of course, patients always have the option to observe which may or may not be in line with their doctor's recommendations.

Dr. Phillip Koo: So you know that was a great summary, and when we talk about radiation, oftentimes we hear so many different letters. “SBRT,” “EBRT,” “protons this.” In this setting with biochemical recurrence, do patients need to sort of ask or look for a specific radiation? Or is it all kind of the same?

Dr. Leslie Ballas: Well, there are a lot of letters that's for sure. You know the most–I think one of them, intensity modulated radiation therapy, IMRT, is used almost universally for prostate cancer around the country. So that's sort of like level set, the basics.

And then there's all these other things. Are you using image guidance, IGRT? Meaning, do you, like, localize your radiation based on what you see and where, you know, you're targeting the radiation. That is also pretty commonplace across the board.
In terms of whether or not to use protons, I mean, you can't live in a town that has a proton machine within like a hundred miles and not hear it on the radio that protons are like, the greatest.

There's not good data in the post-operative space for the use of protons. And honestly, this past year, there was a trial that was presented at our annual meeting, comparing protons versus photons (or regular radiation) in patients who have their prostate in their body, and there was no difference in terms of cancer control.

So protons are great for certain diseases. It's hard for me to push hard for protons in this particular disease, and certainly in the post-op setting there's no data.

The one thing that I would tell patients is that like, when you have your prostate in your body, brachytherapy, the internal placement of either seeds or needles is commonly an option. When there's nothing there anymore, the prostate's been removed, brachytherapy is rarely an option for patients. So that's one thing I think they can kind of take off the table.

Dr. Phillip Koo: Alright good. So, Jason, from a surgical perspective, what interventions can you do for these patients who need salvage?

Dr. Jason Hafron: Yeah, I mean, there are–you can do salvage lymphadenectomies if you see a lymph node recurrence. So there is some surgical resection that you can do.

But in my practice, to be honest with you, I generally think that–and this is my opinion–I typically don't chase recurrences surgically. I think that the radiation oncologist can get better coverage, because even if you see one area, it's really hard surgically to resect, or clean out the pelvis, and with radiation therapy you can get broader, better coverage.

So I kind of don't do that a lot, but it is an option, and there are some centers with experience with that. But I would say most people in this country would not do a surgical approach, would strongly consider radiation therapy.

Dr. Phillip Koo: Great. Alright. So let's talk a little bit about systemic therapy in these patients who have recurrence after a prostatectomy. What's your approach to hormones? Those advanced second-generation hormones? Just tell us–walk us through that.

Dr. Jason Hafron: The way I look at it, and I think Leslie touched on it, it is an option, but I think what the way I–kind of generalizing, try to keep it simple–is that we try to exhaust all pelvic treatments, exhaust all of our radiation options, exhaust all our surgical options before we would consider systemic.

Once we've exhausted our pelvic therapies, then that patient is a potential systemic therapy candidate. There was recently a trial, it's called the EMBARK trial. It's one of my favorite trials. I love the design, the questions that it answered, but it really looked at using ADT plus enzalutamide, or enzalutamide alone in patients after biochemical recurrence.

And we'll go into it further. But I think the key stratifying thing that you have to realize, it's not for everybody. And this is kind of how we open this up, is that not every BCR needs to be treated. And the critical, you know, differentiator or stratifying, who gets treated and not, is the PSA doubling time.

And if the PSA doubling time is less than 9 months, based on the EMBARK data, patients do benefit from treat - systemic therapy. If your doubling time is 12, 15 months, you'd probably be

fine and never need treatment…still need to be followed, but that's kind of like simplified, really, how, you know, I think most urologists have gravitated towards the EMBARK data and applying it. Leslie, what do you think?

Dr. Leslie Ballas: I agree, I think EMBARK was a really impressive trial and looked at the highest risk patients, those that had that doubling time of less than or equal to 9 months, or those who had specific PSA values either after radiation or prostatectomy.

The one thing that I would say is obviously the EMBARK trial didn't have a “no hormone therapy” arms, because it is the highest risk group. And so when I think about hormone therapy for my patients that I'm seeing after surgery, we don't use doubling time for our like, you know, sort of–some of these lower risk patients.

We would use a PSA value. There's data from radiation oncology, national research organization trials that have been run that show that there's a benefit to adding hormone therapy to radiation in the post-op setting. Certainly, if the PSA is above 0.6, when you're in that range of 0.2 to 0.6, that's when I would use genomic testing to help me determine when to use hormone therapy. But in that setting, it's just first generation hormone therapy, Lupron, relugolix, and not necessarily adding another second generation hormone therapy like enzalutamide or abiraterone acetate. These are just drug names, but that some patients obviously have to learn about. But so I would say that the use of hormone therapy depends on– in certain early settings, PSA. And then definitely, as Jason said, in our highest-risk patients, doubling time plays a really big role in that.

Dr. Phillip Koo: Great, you know. So I think there are clearly some you know, nuances here, different approaches as regards to the PSA levels. But you know, ADT and those other androgen drugs have a role. It's just a matter of making sure it's appropriate.

Dr. Jason Hafron: Phil, sorry to interrupt. But I think one critical point about, you know, using systemic therapy, and this is based again on the EMBARK trial, is that there is a drug holiday. So typically in the patients with aggressive doubling time less than 9 months, we can–we treat for 9 months, and if they zero out, the PSA goes back to zero, we can stop therapy and watch them.

And that's huge for patients, because patients will always ask me, “How long do I need to stay on this drug?” Here I have good level one evidence that says you only have to stay on it, if you do well, and in 9 months you're zero we'll stop it.

And when you look at the results of the EMBARK trial, you get almost 2 years of no drug treatment. So we can kind of do this starting and stopping, only treat with these drugs as needed, which I think is very important in this space, that we don't have to overtreat, or leave patients on drugs forever, which is great as a physician, and great for our patients.

Dr. Phillip Koo: You know, I think that's a great point to emphasize. We don't want our patients on drugs indefinitely. I think if we could have a stop time, and they could enjoy without having the the toxicity and financial toxicity of these drugs the better. So good.

Dr. Leslie Ballas: I'm so sorry. Just because I want to just be super clear. We are talking here about post-operative radiation and the addition of hormone therapy based on PSA, or maybe later based on PSA doubling time, in lymph-node **negative** patients. So patients who go to

surgery and all of their lymph nodes that were sampled are **negative**, or they don't have disease in the lymph nodes at the time of PSMA PET.

That is a very different category and different set of recommendations if your lymph nodes were either positive at surgery, or were positive on a PET. So I feel like what we're saying is very valid and very true in the lymph-node negative population.

Dr. Phillip Koo: Correct. That's a good point to highlight, you know, if the disease is outside of the prostate and has gone to lymph nodes, then the discussion changes completely. So make sure the patients remember that.

So we're going to shift gears a little and talk about the patient who's received radiation as their primary therapy. You know they're being followed. So how would you follow that patient, Leslie? Because you just treated them. Give us your sort of follow-up strategy for those patients.

Dr. Leslie Ballas: Yeah, so very similar to how Jason described his post-surgical follow up, we would get PSA every 3 months for the first year, and then go to PSA every 6 months for, you know, years, 2 to 5, probably. You could argue to space it out to once a year, maybe, you know, year 3, but I think it's also important that some patients who get primary radiation get radiation alone, and some patients get radiation and hormone therapy.

For those that get radiation and hormone therapy, and are either getting a shot every 3 months as part of their therapy, or are on continuous hormone therapy with a tablet, we will get a PSA every 3 months while on hormone therapy. So if that lasts beyond that first year, which it can in high-risk patients, we would continue that every-3-month pace.

Dr. Phillip Koo: All right. So oh, go ahead. Sorry. So you're following this patient closely. At what point do you say, “Alright, they are now biochemically recurrent”?

Dr. Leslie Ballas: So we would say that you're biochemically recurrent at a value of 2 plus whatever the lowest value that you got to after radiation, which we call the nadir. So 2 plus nadir would be the definition of biochemical recurrence. So, for example, a patient gets radiation and their PSA goes–-and this is, for you know, without hormones–so the patient goes down to a PSA of 0.5. They don't have recurrence until their PSA is 2.5.

Dr. Phillip Koo: Alright. So what's your approach to getting a PSMA PET and MRI in these patients? You know, there's a lot of discussions, nadir plus 2. Do you do it before? Are you more aggressive? Do you wait until 2, you know?

Dr. Leslie Ballas: This is a really tough question, Phil, and obviously a nuclear medicine physician would be right at the forefront of these kinds of questions. There was recently a publication from UCLA that did a lot of PSMA work that looked at, you know, sort of when is a good time to get PSMA and they noticed that, in terms of like time from radiation, that the PSMAs that they got in the like early stages weren't necessarily representative, because the prostate's still in the body, and maybe all the cells, the prostate cancer cells, hadn't died off or were still taking up PSMA. And so they sort of say that the nadir, in terms of like the lowest level, and when the PSMA starts to be most accurate, would be at like 9 to 12 months after radiation.

And so I typically try not to get one before that. If God forbid, a patient has recurrence, obviously, if they start having a very fast doubling time, again that sort of thing that Jason was talking about, that might change the equation and not necessarily make me wait. But I've been reasonably good about waiting the 12 months or so in patients, and then certainly trying to get them, as, you know, at least to about 1 plus nadir. But that's practice pattern.

Dr. Phillip Koo: Sure. And is it safe to say you're doing that, again, because you want to be more aggressive and know sooner, so you could intervene sooner?

Dr. Leslie Ballas: I do, but it's really tricky when the prostate's still in the body to get a PSMA PET scan, because, obviously, normal prostate tissue also can take up PSMA. And so I do try to wait as long as it seems appropriate, in terms of patient care.

To answer the question that we had previously talked about is, if the PSMA PET is positive in the prostate, we would typically get an MRI as well because we do want to biopsy and make sure that there's actual disease there. And MRI directs the biopsy location. We don't just use PSMA PET to call a true recurrence in the prostate gland. Jason, have you been doing similar things when you're asked to biopsy?

Dr. Jason Hafron: Yeah, I mean, PSMA PET was never validated, really, in the prostate. So it can be unreliable. And if we're going to do additional treatment, especially some sort of ablation or adjuvant salvage treatment, we always use a biopsy.

Dr. Phillip Koo: So, Leslie, let's say that you get the PSMA PET and it's negative. There's nothing in the prostate. What do you do then?

Dr. Leslie Ballas: And there's–and they're having their 2 plus nadir at that point they don't really [inaudible] recurrence.

Dr. Phillip Koo: Let's say they're 1 plus nadir, 2 plus nadir. They're yeah–they're sort of creeping up.

Dr. Leslie Ballas: Yeah, I guess, I think that is always a multidisciplinary discussion. We would discuss these patients with our urologists and say, “Hey, you know, nothing there.” We would probably still get an MRI of the prostate, just to make sure that, like, PSMA isn't missing something that should be biopsied. But then we would start talking about salvage options for patients.

Dr. Phillip Koo: Great. So let's–perfect segue. What are our salvage options? We'll start with you, and then we'll go to Jason.

Dr. Leslie Ballas: So the salvage options are salvage prostatectomy or removal of well–first of all, I think it's really important to separate this out.
So, if the recurrence is only in the prostate and nowhere else, then the options are salvage prostatectomy–removal of the prostate gland, brachytherapy–implantation typically of needles into the prostate gland, or, and this isn't my favorite, but that's, you know, Jason will get, maybe get into it, would be some form of focal ablation–HIFU, cryotherapy, some of these, you know, sort of focal treatments.

If the disease has spread beyond the prostate and it's in the pelvic lymph nodes, then patient may have options for further external radiation. There may be surgical options. There's certainly hormone options. I mean, there are so many branches to that tree, once we get beyond just the prostate.

Dr. Phillip Koo: All right, good. So before I go to Jason, I think, you know, re-irradiating the prostate is not an option.

Dr. Leslie Ballas: So that is a common thing that we get asked, and re-irradiation of the prostate with external radiation, IMRT, some of those fancy letters we talked about, that is typically not an option.
Re-irradiation of the prostate with brachytherapy, internal implantation of radiation, typically with needles, is actually one of the preferred methods of treating a prostate that has recurrence that's previously been radiated, because it has the least urinary side effects associated with it.

Dr. Phillip Koo: Alright. That's a great point to take home. So alright. Good. So I think you created a very good distinct line between those that are just in the prostate, the recurrence, versus those that it's spread outside. And I agree it gets more complicated. We didn't talk about mets-directed therapy and other systemic treatments, but we will in a different webinar.

So Jason, as a surgeon, from what I hear, going in and taking out the prostate after it's gotten radiation is not the most simple surgery. But tell me your approach.

Dr. Jason Hafron: Yeah, I mean, a salvage robotic prostatectomy is not a common operation. I mean, I'll do a handful of them per, you know, a year. It's a different discussion, you know. It's a different discussion than we would have if we were doing a primary prostatectomy. It is associated with some morbidity.

There's a high risk of incontinence. Erection sparing, or nerve sparing is almost impossible, but it is an option, and generally, you know, we don't have rigid guidelines. But if there is a young patient who's received radiation, you know, we would consider a salvage prostatectomy in those patients. But, generally speaking, most patients would get, you know, adjuvant or salvage, brachytherapy, or some of these salvage ablative technologies that Leslie touched on. We do a lot of those now, and I think there's been a significant improvement in this technology which is really based on the improvement in our imaging, so that we are doing more focal salvage therapies because we can identify the lesion. You know, biopsy that lesion, confirm it on PET and really zone in.

And those you know, those options are cryoablation. Cryoablation has been around for 20 years. It's very effective. We have focal HIFU, high intensity frequency ultrasound. We can give, you know, through the penis or through the rectum, is very effective.

We have a newer modality called Nanoknife, that uses electrical energy to ablate the tissue. But they're all very effective. They all work well, and you know they can–you know, I quote my patients about 55% to 60% success rate, that we can get them out of this situation. And the key with these ablative technologies is that we can avoid hormone therapy, or at least delay it. So if we have a young guy, we can do a surgical procedure, and really delay that ADT or androgen deprivation therapy, and all the side effects associated with that.

Dr. Phillip Koo: Great. Thank you. So, going back to this patient, post-radiation they recur. Leslie, we've talked about systemic therapies, let's say, is there any nuance here in this patient that is different from what we discussed earlier?

Dr. Leslie Ballas: I mean, I think just that we wouldn't–I mean, I think the difference is, as sort of we just described, that we would typically use brachytherapy if it was limited to the prostate. You know, there's lots of radiation options if they've had prior radiation to the prostate, and they just have a recurrence in one of their lymph nodes, we can still give external radiation in that setting.

You know, I think in today's day and age, we don't have great studies telling us exactly how many patients only recur in the prostate, but that seems to be sort of the minority of patients. If patients are recurring after radiation, most typically, they're recurring outside of the prostate. And so again, that's when we have lots of different options.

Dr. Phillip Koo: All right. Good. And that's where hormones come into play. All those other more advanced drugs. So good.

So we have some time for Q and A. One question that comes up multiple times is, “What can I do after I get my primary radiation or surgery to help prevent this?” And oftentimes we think about nutrition, exercise, sleep, things like that. What are your thoughts here?

Dr. Jason Hafron: I think all of those are important. I mean, we don't have solid data to support it. But there is soft data to support, you know, being healthy will lead to better outcomes. Obesity, red meat, smoking are all associated with poorer outcomes. So what I tell my patients is, you know, you need to exercise. You need to keep your weight in a good range.

And I try to get my patients to follow a Mediterranean diet. Chicken, fish, fruits, vegetables, no fried foods, no fast food. Limit your red meat for special occasions, limit your dairy, limit your smoked pork products. Things like that, I think, really will have some impact on your disease. Can I quantify it? No.

But the other part of this is, if you look at most cases of prostate cancer, most patients will die of cardiovascular disease. So if we're really being good physicians and good stewards of health, we want our patients as healthy as possible, because that's probably their greatest risk when you put it all together.

Dr. Leslie Ballas: I tell them the same thing, Jason. I always say that the greatest killer of Americans is heart disease. So eat heart-healthy and get your PSA checked regularly. Like. that's what you can do.

Dr. Jason Hafron: Yeah, well said.

Dr. Phillip Koo: Great. I think these are all great points. And I think at minimum, if you're eating better and exercising, you're going to feel better regardless. And yes, you're decreasing your risk for heart disease.

So, Leslie, this question has come up several times. Those technologies that create the space in between the bladder and rectum. What role do those technologies have in the biochemical recurring, not initial.

Dr. Leslie Ballas: So once a patient's had–so I guess first of all, those products can be important in the intact prostate setting. So if you're getting primary radiation, they get–it's like a little balloon, or some, you know, water-based jelly that gets inserted into a little potential space or a little plane in between the prostate and the rectum.

In truth, we don't use those all the time anymore, because we have found that the side effects from them have been somewhat underreported. And this is actually like, well-documented, and also because the latest data showing Grade 3 - or needing medical intervention - to the rectum after good quality modern radiation is 0.5%. So now you're taking on another procedure, another risk to diminish your potential toxicity to the rectum of less than 0.5%. So there's a lot that goes into that question up front.

But in the salvage setting, after someone's had surgery, that little space where the balloon or the water-based gel would go, has been obliterated. So there is no proven benefit to putting that in afterwards, and if certainly–if we don't recommend it, because there's nowhere for it to go. It would just sort of like, diffuse broadly into the pelvis.

Dr. Phillip Koo: Great. Thank you. So talking about biochemical recurrence, this question came up a couple of times.

So you know, Jason, after a prostatectomy, you expect the PSA to go to undetectable. Is there sort of an expectation, Leslie, when you do radiation with regards to how low it goes, and if it doesn't, what does it tell you, if it only goes to a certain level?

Dr. Leslie Ballas: Yeah, so this is something that's harder for patients necessarily to accept. But you know, we would want the PSA, we typically would love it to be less than 0.5 after radiation to the prostate. Less than 1, I think, is good. We want it to reach its lowest point, and not rise consistently. That's really what you want.

Dr. Phillip Koo: All right. So you know, we've talked a little about this, but in the recurrent setting it could rise and decrease. What are some reasons why it sort of fluctuates? And you know you mentioned 3, Leslie, Jason sort of from a urologic surgeon perspective. What's your approach to this PSA?

Dr. Jason Hafron: Yeah, I think PSA is a great test, but it's not perfect. And there's other reasons why it can rise. And if you still–if a man still has a prostate, they've received adequate radiation, it can go up for other reasons. It can go up for recent ejaculation, heavy exercise, excessive bike riding. If they've had a recent UTI, or they've had a recent procedure. Anything that stimulates or angers the prostate, even in a radiated prostate, you can see a rise. So I think the key, and Leslie touched on this in the beginning, is we never go chase one PSA value.

We would like to see 1. Maybe it's a fluke. Maybe it's a lab error. Who knows? And so we like to, you know, check it in a few weeks or a month later to see if this is real, or rule out any other causes besides a true BCR. So you've got to be careful. PSA is a trap, and it can be tricky. You've got to look at it in a couple time points.

Dr. Phillip Koo: Great. Leslie, anything you want to add here?

Dr. Leslie Ballas: No, I agree with what Jason said. I think that we know as radiation oncologists that there is a phenomenon called a PSA bounce. It can happen at like 18 months after treatment, it could be for any one of the things that Jason listed. It also could be for, you know, like, there's lots of things that can cause it. But yeah, I agree with what Jason said.

Dr. Phillip Koo: Great. So you know, we talked a little bit about this trial called EMBARK. In general when clinical trials design, I think we'd love to be able to prove that it helps patients live longer. But that's not always feasible for a variety of reasons. And we have these–what we call surrogate endpoints, and always lots of discussion around sort of these goals that sort of fall in between overall survival and something else, and recurrence, let's say, or progression. So, Leslie, what sort of–help demystify this for a lot of our listeners who sometimes read these articles and read a lot about this topic online.

Dr. Leslie Ballas: So, I think it's really important to understand that when you have a clinical trial and your endpoint is overall survival, which is what most people are kind of thinking about in their heads, they forget that overall survival means that, you know, if a patient dies of a heart attack, that it counts against overall survival. We are talking about a patient population that is, on average, 67 years of age. They have lived a life that allows them to have other medical comorbidities, and so things that could possibly take their life that are totally unrelated to prostate cancer, affect overall survival as an outcome in clinical trials.

That being said, obviously, we also want to know what overall survival is, because that's important in studying these new medications or new treatments. But another thing to note is that overall survival can take–I mean, we're talking about prostate cancer. And, God willing, this is a slow-growing disease in many patients, and so therefore can take 15, 20 years to report out. And so by the time you report out a trial 15, 20 years later, there's new drugs, new imaging, new everything on the market, and it sometimes doesn't jive with where we are clinically and practically.

And so, therefore, because of those couple of things, clinical trialists will sometimes come up with what we call surrogate endpoints or other things that are interesting and important to patients that might either predict for overall survival, or are important for patients to understand. The EMBARK trial used metastasis-free survival as its endpoint. Meaning what is the chance you are alive and don't have a prostate cancer metastasis, disease outside of your prostate?

That's a super important endpoint. Patients want to know, “Oh, my gosh! Is it going to spread? Am I going to have pain from, you know, disease outside of my prostate?” And metastasis-free survival is a good predictor of how overall survival will look. And so that is kind of what we mean by surrogate endpoint, and why we evaluate them.

Dr. Phillip Koo: That's great. Thank you. So we're almost at the top of the hour. Jason, any closing last words from you?

Dr. Jason Hafron: Yeah, I think that, the key message, and hopefully, this came across tonight, is that BCR is not a death sentence. BCR may or may not have to be treated, and that we have a lot of great treatment options that can make prostate cancer not as bad as you would appear. So that we do have good interventions. But just because you have a BCR doesn't mean it's over, and it doesn't necessarily mean you need to be treated.
But if you do need to be treated, we do have a lot of great options that we highlighted. And it's important, like, you know, Phil, you said you’ve got to work in the multidisciplinary team with all -

your oncologist, your uro-oncologist, your radio-oncologist, to find the best option for your situation.

Dr. Phillip Koo: Great. Leslie, final words?

Dr. Leslie Ballas: Yeah, I guess, in sort of part and parcel with what Jason's saying, when we treat someone after surgery with radiation, that treatment is intended to be curative. Meaning you still have a chance at cure of your prostate cancer, if, you know, with some of these secondary salvage treatments. And so I would say, just don't give up hope.

Dr. Phillip Koo: That's wonderful. And in a future webinar, we are going to touch on the topic of when you have biochemical recurrence and the disease is outside of your prostate. Maybe it's gone to nodes or bones, or what else, and that's a whole different other topic, and it will require two, three hours but we'll try to get it into one.

So be on the lookout for your email. Becky will send out invitations for that as well, so be sure to register. Thank you guys so much. It was very enlightening. I learned a lot. So appreciate your time.

Dr. Leslie Ballas: Thank you so much.

Dr. Jason Hafron: Yeah, thank you. Appreciate it.

Dr. Phillip Koo: Take care!