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Hello, everyone. Thank you for joining us tonight for our webinar on advanced prostate cancer, focusing on metastatic hormone sensitive disease. We're going to be doing a couple of sessions on this topic, this very important topic, and I am the moderator, William O. I'm the chief medical officer for PCF. I will point out that this this webinar is supported by Lantheus and we thank them for their support of this event.

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But just a reminder that all views expressed during this webinar are really those of the speakers. Just want to make a couple of points about Prostate Cancer Foundation. We were founded 30 years ago with the mission to reduce death and suffering from prostate cancer. We found the most promising research with a global footprint in 28 countries. Many young investigators and some of the best scientists in the field have been really supported by PCF as and have received early stage funding that have led to many of the therapies we know about and we'll be talking about today.

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We also have a lot of resources for patients and their families. So I encourage you to go to PCF Talk. We have multiple free guidelines that you can guides that you can actually download. You can register for our next webinar and view past webinars and join an online support group. In addition, we recently launched a new website called Prostate Cancer Patient Voices.

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This has a lot of outstanding video of men who have gone through the diagnosis and treatment for prostate cancer and sharing their personal experiences. So I encourage you to go to that website as well. I mentioned that we will have a second part to this series on November 14th with two very distinguished oncologists talking about what's called metastatic castration resistant prostate cancer.

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Today we're going to focus on hormone sensitive prostate cancer, and we will define this in the next few minutes. But please sign in to see Dr. Taplin and Dr. Mackay at that time. So just as I want to point out how the PCF mission is really had such an impact on the disease. We've funded in 2020 to 50 research projects totaling \$30 million, and we have the opportunity for you as somebody interested in this disease and impacting this disease to really have an impact by by potentially donating.

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So think about us as you think of your end of your charitable giving. So as I said, we have two of the most important and distinguished clinicians and investigators in the field of prostate cancer. Joining us tonight. The first is Oliver Sartor, a medical oncologist and the Division of Medical Oncology at Mayo Clinic. He's really an internationally recognized expert, published over 500 articles and is about to go to Europe to present more important data on the newest therapies and PSA radial ligands.

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He's led four pivotal trials that have led to drugs, FDA approval and drugs that are FDA approved and have served in very important leadership roles. Our other speaker tonight is Neil Shaw. He's the medical director of the Carolina Urologic Research Center and the chief medical officer for Strategic growth for Genesis Care. He's also incredibly distinguished with more than 400 clinical trials and 350 papers.

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He has a New England Journal paper out just this past week and has really been an important investigator in understanding the outcomes for prostate cancer. So I'll ask Dr. Sartor and Dr. Shaw to join us. Now to both turn on your turn on your sound as well. We're going to try to make this as interactive as possible, but I thought I would just start by giving a little bit of background for the audience about what we're talking about and some of the definitions, and I'll stop along the way and ask you both to comment on this concept of metastatic hormone sensitive disease.

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The first is this model that we've all seen many times. So some of the patients, some of the people on this call may understand that prostate cancer presents in the prostate and may have surgery, radiation and may be cured of the disease. But unfortunately, some patients do progress and they move to the state that I circled here called metastatic hormone sensitive.

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So I wanted to have maybe, Neal, talk a little bit about how you define hormone sensitive prostate cancer. Yeah, Thank you very much, William. It's a great pleasure to be here with Oliver and you. And on behalf of the folks at PCF. Fantastic work that you all been doing for decades now. You know, funding, great research and education for four

patients.

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Yeah. So we use this word sensitive. Well, let me take it back. Metastatic as a as a sort of a long poly syllabic word of saying that the disease has spread outside the prostate and prostate cancer has had this remarkable predilection more than any other cancer, solid cancer, solid tumor to go to bones. Now, we're not entirely sure why that is, but it just has a big propensity to go to bones.

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But it can also go to the lymph nodes and it can go to other organs so that by definition, that defines the has historical definition of metastatic. Based upon that, the conventional imaging that we use called CT scans and bone scans an important thing that's happened in the last couple of years is we've gotten better with our imaging technologies.

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So we have these newer imaging modality is called PSA, a pet, which is very important because it picks up locations of cancer, prostate cancer, specifically, where oftentimes conventional CT scans and bone scans couldn't find it. Now, when we talk about hormone sensitive, which is the focus today as opposed to resistant, I think for if I'm a patient, a patient family member, it's sort of this biologic inflection point, which means when we're able to lower male hormone testosterone and one of the key metabolites of the testosterone called dihydrotestosterone and I know you have a slide coming up, this discovery led to a Nobel Prize, but which is it's so cool in that that's the two urologists

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who got Nobel Prizes. The first one was this gentleman, Professor Huggins. And so the notion is, is that if you lower the male hormone and you get it down to a very, very low level, 95% plus of prostate cancer cells, when the disease has spread, we'll go into remission. And then what happens over a period of time. And I think your next program is going to talk about this with doctors Taplin and Mackay, which is probably going to be a phenomenal program.

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It's called Resistance. In other words, we've lowered the testosterone level, but now the PSA is going up, it's rising, and that historically has defined what we call resistance, and that opens up a whole new armament area of therapies. And so I think and you see that in this

very nice disease states, clinical states diagram that you have here at the end of the day, I think among patient, you want to recognize that you want to keep patients in the sensitive middle you for as long as possible because once you go and become resistant, the cancer is selecting out clones that are becoming more difficult to treat.

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Thank you, Neal. It's really helpful. Oliver, I want to ask you to comment on two things. One, this duration that I put on the bottom of this slide, is this an exaggeration? How long are men with prostate cancer living? And you know, how how what do patients expect in terms of the long term prognosis for prostate cancer? And in a way, it really depends when you're diagnosed.

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And one of the things that we've learned is that things like PSA testing can actually introduce an earlier detection than you might have otherwise had. If you go to the pre PSA era, there was one set of statistics that in the post PSA era, which really started around 1990, you end up with more. And that's because what I would call a lead time bias.

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You diagnosed prostate cancer earlier when you use a PSA. Now, if you're using this sort of clinically localized rising PSA, moving on to metastatic hormone sensitive and then moving even beyond that to castrate resistant, you know, 10 to 20 years is pretty reasonable. But if you're presenting with high volume metastatic disease at the time you're diagnosed, that is completely disdain from somebody who may be coming in with Gleason six, which may not even need to be treated if it's confined to the prostate.

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So one of the things that I want to emphasize to my patients is the extraordinary heterogeneity of this disease. And then not everybody has good disease and not everybody has bad disease. You kind of have your disease. And it depends on the stage in the Gleason and how much you are having symptoms, whether or not you have a problems with what we call performance status, how high the PSA is.

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So, so many variables go into prognosis that I try to individualized it, to be honest. Thank you. Yeah, I think I think this is the most important message here is that patients with prostate cancer, even with cancer that may relapse and it could be in the bones or lymph

nodes or elsewhere. It can still live for many years.

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This is not a disease of weeks or months on on average, it's really a disease of years and sometimes decades. Many of us have patients who we've taken care of for many, many years and even decades. And and as the new treatments come in, we know that patients are living longer and longer. Neal, I wanted to ask you to comment on just this this slide, the concept of a multidisciplinary approach.

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Your urologist, Oliver, is an oncologist, as am I. There are other doctors and other people involved. Can you just talk about why this is important? Yeah, this is enormously important. And in the arc of my career, you know, I finished my training and started in practice in 1990. And there used to be, I think, unfortunately, a amongst specialties between community and academia, this sort of, you know, rivalry, so to speak, and a real lack of of collegiality, turf battles.

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And I think it affected in for a while, you know, patients finding who they could go to for trust and who to rely upon, which actually was as a separate issue, this whole notion now around public trust. But I want to comment upon that later and why I think PCF is so important, because it's really a bastion of trust and a lot of folks have a really hard time finding trusted sites.

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We see this not only in health care but in politics and so many other things. Where do you find a trusted resource? I think PCF is is that level. But having said that, I love this Venn diagram because it brings together first and foremost who's at the center. It's the patient, the North Star of what everything we do must be towards benefiting patients, approved therapies, clinical trials, and that's how we need to work.

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You see, urologist, radiation oncologist, met oncologist. And as you say, William, what's now part of this multidisciplinary team are nuclear medicine, radiologists, pathologists, interventional radiologists, primary care physicians, cardiologists, neurologists. Because cardio oncology, neuro oncology really important. And under the AHP, the allied health care professionals, those are all the non physicians that are so key in the nurses, the physician assistants,

nurse practitioners, everyone, the entire team, the the folks who help do the pre-authorization so patients can get their drugs paid for, you know, social services, physical therapy, you know, dealing with the stress and, you know, and social and psychological issues, nutritionists.

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So I think what's really great, despite the fact that health care and our health care, you know, ecosystem is become more complicated and clearly more bureaucratic is we have so many more people who really understand the value proposition for multidisciplinary work to provide patients the optimal care. And there should not be this, you know, internecine warfare. Everybody should be working together.

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So I love a diagram like this. And I think it's it's it's really evolved nicely over the course of my career. Well, thank you, Neal. Oliver, any comments about working with urologists and and nurses and others who are really important in the care of these patients? You know, I think Neal summarized it well. I do think in this is maybe a point that I would bring from my perspective.

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You do need a quarterback and the quarterback is going to be the one that is ultimately going to coordinate the care. And at times that can be somebody like Neal Shaw is the biologist who really understands the culture just from a framework. At times it can be a medical oncologist, and even though there are many contributors to the care, you still need sort of a center so that you not just bouncing from specialists to specialist, but you have an overall plan that will help carry you forward that may involve multiple specialties, including, as Neal mentioned, nuclear medicine, pathology, molecular pathology, genetics, things that you may not have considered four or five years ago are now

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at the heart of the prostate cancer patient. Yeah, really, really good advice. We talked about this slide. I'm not going to focus too much on it except to tell everyone two Nobel Prizes have been award reported for prostate cancer. The original observation that testosterone allows this cancer to grow and then the actual chemical production of the first analog called Lupron, which some of the patients, some of the people on this call will actually be treated with.

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There are some new oral and injectable antagonists that have recently come out, and we may talk a little bit about it as we move on in the case. But the most important thing is androgen deprivation, therapy or lowering testosterone is the key. So I'm going to show one more slide, which is, I realize, a little bit complicated, and we can certainly share this slide with the audience.

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This is also going to be taped and put online. And I know people are going to ask questions and feel free to ask questions. But what this this diagram shows is the kind of the the natural history and pathway of of a typical patient with metastatic or advanced prostate cancer. Obviously, if you have surgery or radiation and the cancer never comes back, you never move towards the right on this graph.

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You just your cancer is cured. But patients who do have recurrence, they go through these stages of treatment. And as I said, this dark blue area, we're going to focus on in a future in a future webinar. But for now, we're going to focus on this area, which is what we call hormone sensitive metastatic prostate cancer. And and again, what's on on the x axis here is really the the time.

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And on the Y axis, PSA is kind of a surrogate for for the burden of disease. And I think, you know, it looks very complicated. I tried to color code this with different colors based on the type of drugs that they are. But in the end, I think what we want to do maybe is drill into a case, because I think this is one patient's story.

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It's an amalgamation of many patients that that I know the three of us have taken care of. And and it may resonate with some of the people listening in there as Oliver and both of you said, every person's unique. But people fall into categories where we as physicians can help these patients and their families negotiate the best therapeutic approaches to give them the best length of life and quality of life.

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And so let me just go over this and get your thoughts along the way, because I think it brings up a lot of important questions. This is a 59 year old man who presents with urinary retention, and that means he wasn't able to really pee very well. He had tiredness or appetite. He was he's a widower with high blood pressure and high cholesterol.

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And this is the first time he has a PSA and it's very, very high. 150. He gets a biopsy which shows Gleason score of eight, which is a high risk prostate cancer and all of his course. And he has scans that are negative, actually, in this case, he has no family history of prostate cancer. He has surgery robotically.

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That and his PSA actually has a very, very nice response. It goes all the way down to almost undetectable levels and about a year later, his PSA has now risen. Now, we don't we don't have any history in between, but it's now up to 25. So it went from very low up to 25 again. And now he has a CTN bone scan.

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We're going to talk a little bit about imaging, but this is a person who was diagnosed a few years ago now, and he has at least seven spots or metastatic lesions in his bones, in his lumbar spine, his pelvis and his ribs. And he is symptomatic, meaning he has symptoms of pain and also fatigue. He has not had any genetic testing.

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We'll talk about that in a minute. When I go back to you guys. All right. So the first question is, should he start androgen deprivation therapy, as I showed in that graph? And if so, which one? Neal? Yeah, So well, this such an interesting case, if I could just comment. I mean, the fact that he underwent a process detect me with that super high PSA a and very aggressive prostate cancer.

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You know, it would have been really nice to see if he would have gotten one of the, you know, the newer PSA pet scans, because it would have almost assuredly had been positive and might have been, you know, lordly positive and so might have had him avoid the surgery is a young man. So I understand why aggressive treatment maybe was chosen.

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But I would have been a nice opportunity for the PSA pet. So having said that, the answer is is yeah, we use ADT or androgen deprivation therapy, we always say, and almost every one of our our articles, you know, for patients who have advanced diseases, this man does and technically he would be considered high volume because he has when we have some arbitrary distinctions about this four or more lesions on conventional imaging.

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He has seven and it's in his axial spine. The main spine is the cervical thoracic lumbar spine and also what we call appendage killer outside of the axial spine. So by having four or more lesions, at least one outside the axial spine, he's considered high volume. But even at low volume, he would be a candidate for testosterone suppression.

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You know, it's controversial how you started the the end game is to get the testosterone level below a certain number. We use this 50 native gram per deciliter cutoff where testosterone levels are typically between 308 hundred, depending upon the lab you're using. And the and we've had historically we Huggins that Nobel Prize, you know, he got it for you know when men he just removed men's testicles and and nobody really wants to have that done for clear reasons.

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And so these drugs were invented in the eighties where you can inject under the skin or in the muscle called La H agonists, which are a little bit counterintuitive because they don't work immediately. There's a bit of a two week delay before they actually achieve what they're trying to achieve, which is the suppression. But it has to do with the way the formulations were in safety.

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And it wasn't till around 2008 that we saw the really the first significant approval of a drug called an antagonist as opposed to an agonist which didn't have that two week surge in the testosterone. And and then ultimately what happened There you go, 2008. And then 12 years later, we have an oral drug, a pill that is an antagonist as opposed to an agonist.

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So the mechanism of action makes clearly just makes more sense. I don't think anybody argues that. But for nearly 50 years now, we've had these agonists and you could get it in injection under the skin or in the muscle. One month, three month, four months, six months. So they've been around a long time and they're very effective. It just comes down to, do you want to take a pill?

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Do you want to take a shot? Do you want to? There are some cost

issues. And then in our our paper, which we published and presented, there is some suggestion that there could be some improvement in cardiovascular safety. It's controversial and there are some additional trials that are investigating that this. Can you mean what these you mean with these antagonists that the antagonists value garlic's or the garlic's might actually have a favorable cardiovascular profile?

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Unknown

That's correct. That's correct. And and so but we still don't have the perfect evidence for that. So there are prospective trials that are ongoing and there have been a lot of papers published on this but still point controversy. So it's particularly something to discuss. You know, I think one of the things that Oliver would agree and you as well, William and PCP patient choice patients need to have a full throated discussion again with their clinician, their clinician team of all of the options.

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So that is this very important notion around shared decision making. And at the heart of it, getting back to your Venn diagram is the patient needs to be able to understand why would I pick an agonist over an antagonist at the end of the decade? That patient has to be started on that. I'll stop with that because the next question you have on there is really important is adding additional treatment.

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Yeah. Now that's that's a great overview, Neil. And even for the audience, there's a lot of question should I get looped slide, Should I get that garlic, Should I get the new oral therapy? You go and there are other brands that we haven't mentioned, and I do think it's a very personal decision. This man did not have any cardiovascular non disease, but he did have cardiovascular risk.

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So it is something that you have to speak to your doctor about. Oliver addressed the second question. Should he he gets ADT, should he get a second treatment? And if so, should it be chemotherapy? Should it be a so-called RC? If you can describe what that is both you can leave radiation for for the moment. What do you think?

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Yeah, so great, great question. And you know, there a variety of factors that sort of influence this decision. You know the age and comorbid it is being one you know how old you are and what if you're a

39 year old marathon runner versus 98 year old nursing home patient? Well, that can make a difference. The volume of disease can make a difference.

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And then also there's a distinction between those who are initially diagnosed with metastatic disease. And we call those the de novo patients versus the recurrent patients. And the first thing I'm going to say is for patients with metastatic disease today, I always use a second hormone, androgen deprivation, of course, and you can debate about which one, but pretty much in my opinion, they've lower testosterone.

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That's what they do. They don't do anything else. They just slower testosterone. But then I want to concentrate for a brief moment on the energy receptor signaling inhibitors and there are two big classes. One of these inhibits the synthesis of the testosterone, not only within the testicular environment, but also in the adrenal environment. And believe it or not, that the cancer cells themselves can make some testosterone here we have a drug called abiraterone, and it's been FDA approved since 2011.

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And it turns out that abiraterone has been demonstrated to prolong survival for those with metastatic disease would give it in combination with ADT. But there's more to the story. And among those that are to the story are those that block the testosterone from acting. And it turns out there's more than one and there's one called enzalutamide, one called APELIN Demand, one called Darryl Woodbine.

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And each of these are FDA approved drugs. Each with their own little context. But the bottom line is, should somebody who has metastatic disease receive more than one drug? And the answer is almost invariably yes, chemotherapy. I tell you what, I won't go all the way into the chemotherapy. There's some data on triplet. I personally have vastly diminished my chemotherapy use in patients with recurrent as opposed to de novo disease.

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Unknown

Patients like this one did have high volume, but they're not Super high volume is a young patient. But I'll simply say the chemotherapy we get at more discussions. But 80. Yes. Antigen receptor signaling inhibitor, Absolutely. Thank you. Yeah, we can go back to that in a

minute. But I want to cover something that Neil you already brought up which is imaging.

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Imaging has changed dramatically in just the past couple of years in the United States. Really in the last year. Our ability to get smart, pet scans. Can you talk about whether he should have one? Now, remember, he only had a CT scan and a bone scan, traditional imaging, because this was a couple of years ago. Now that he's progressing and with the availability of PSA may PET should he have that?

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And then the second question that we get a lot is if it is positive, should he get this new therapy called value 177? Yeah, super important question. I think that, you know, we have papers that are sort of trying to prioritize the best use for PSA pad. I think for patients who have newly diagnosed disease confined to the prostate, which we tend to refer to as high risk localized prostate cancer.

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And the easiest way, I think, for patients to think about this is we've really changed our scoring system so that when you're diagnosed, there's what's called the grade group and you're either it's simple, it's it's a one, two, three, four or five. And if you have a three an especially a four or five, which are the more aggressive forms of the cancer of the prostate adenocarcinoma, cancer, that's where a PSA pet is extremely important to get the other place where it's really important to get is if you get treatment for your prostate cancer, whether it's surgery, radiation, both or some other form of intervention.

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And you think you've completely treated the prostate area, you've killed all those cancer cells and your PSA is going up and you're conventional imaging is negative. Getting a PSA pad is a is a fantastic test. It's just a lot more accurate with tumor low smaller tumor volumes. I think there is there's debate about getting it for someone like this gentleman.

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Unknown

The one advantage of getting it for someone like him who has seven bone lesions and presumably a CT scan that didn't show any disease, the lungs, the liver or the lymph nodes that could be microscopically found with the PSA pad is that unless there was just a lot of disease, maybe in the liver, which is not going to be that common, but it can

occur, it's probably not going to change your therapy.

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Unknown

And as Oliver said, couplet or doublet therapy is the standard of care now. And even for some patients, it's adding in the chemotherapy or the triplet therapy. We had one reason for getting the PSA pet from an insurance coverage standpoint, and the label is that about 85% of patients will have a pet positivity and if they are psma pet positive later on when they develop resistant disease, they can avail themselves of a new area or another line of therapy.

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We have lots of lines of therapy and you're going to cover it next week. So I don't want to jump the shark, so to speak. Here is these really great things called radio ligand therapy, and particularly one called leftism. And Oliver is actually going to be presenting on this set a major conference in in Madrid called as Mao, you know, this weekend.

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And yeah, I had the privilege of being on the steering committee with them. So it's a it's a really huge advance, but it's not approved yet. Insensitive patients. Yeah. So, Oliver, just to comment on that, because people are hearing about this drug and they're going to hear more about it this week. If he did have a PET scan, would he be eligible now or do you think he'll be eligible in the future is not eligible.

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Now, just to be clear, it's possible in the future, but the trial that is really key for this type of patient who is going to be hormone sensitive and going to be treated with hormone therapy for sure is a trial called the PSA addition. And the main addition trial is not shipment's sure it's fully accrued over 1100 patients, but we don't have any results yet.

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So it's really premature to speculate. We hope it's going to be positive and that would allow this type of patient to potentially receive rotation. But that's premature. We don't have the data in this setting as of yet. Well, thank you. That's very, very helpful. Just as to summarize, Absolutely. This man needs androgen deprivation therapy. And absolutely, we, the two of you agree he should get a second treatment.

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It could include chemo, but it absolutely has to include in our side the decision about chemo is more personal one, but the decision about the side, unless it's an absolute contraindication, and I've personally found very few of the patients should be insisting that their doctors give them an RC. And one reason for that is remember 80 makes your PSA go down.

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The goal here is not just to make your PSA go down, it's to control the cancer for as long as possible. And there have now been eight randomized clinical trials that show that if you add a medicine now, you improve survival, even compared to adding it a little later. So it's very important that patients like this go on at least double it, what we call doublet therapy, a pill at a shot right at the very beginning.

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I to take one quick comment. What got you to such an important point? So one thing is and despite the fact that there are eight phase three global trials, actually there's even more now, if you throw in the two triplet trials that have what we have, we say level one evidence, which is our highest level of evidence and is now in all of our guidelines, National Comprehensive Cancer Network, the EUA, ASCO, as more everybody says, you should be doing doublet therapy and even occasionally triplet therapy.

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And yet despite that, in 2023, we have great, well, unfortunate data, sad data that in the United States alone, maybe at best, 50% of patients are getting doublet therapy. They're still getting the monotherapy, just the ADT alone. And you said it, the ADT alone does a good job of lowering the PSA. And then I think what happens is patients say, oh, look, my PSA went down so low and they the doctor, it's probably a lot of times the urologist says, Oh, yeah, you PSA went down, We're good.

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I'm declaring victory. But your point is so well taken is that by adding in that oral drug, the the androgen receptor blocker, you're getting that marked additional benefit. I mean, there's a little bit more there's more costs. There may be some additional side effects, but there's this level one obvious evidence that will help patients keep them in the sensitive environment longer and also prevents them from, their disease, progressing and becoming resistant and also clear

data that it improves their survival.

00:35:29:15 – 00:35:59:12

Unknown

I'm going to mention one thing really quick. William Sandridge in by code mod. Ah, Flu mod is not the type of therapy we're talking about. And these older are drugs like bipolar to mind and otherwise called Capsid Acts are flu mod called units, and those are not the new drugs we're talking about. The drugs we're talking about are going to be they're allowed on apple insulin or abiraterone.

00:35:59:18 – 00:36:22:16

Unknown

They may be more in the future, but important distinction, you ought to be on two drugs. Thank you for raising the point. What's and we're at home. Yeah, thank you for that, Oliver and Neil. It is so important. It's probably one of the most important take home messages of this call of this webinar is if the doctor doesn't start it, you as the patient really should be insisting on it.

00:36:22:16 – 00:36:44:20

Unknown

A second drug. So let me just go to the next part of this, because we have had so many questions about what's next. So two years later, which is now in the current setting, the patient has had a tremendous response to lupus, light and abiraterone. Again, remember, he started everything a few years back and his PSA went down to zero.

00:36:44:20 – 00:37:13:10

Unknown

A wonderful response. But he's tired. He's missing his sexual function. His muscles feel weak. He's unfortunately a little bit of a potbelly and he wants a break. So let's go back to you, Neil. Can you can he stop treatment safely? So, you know, it's it's really interesting. And so in the arc of our learnings and certainly in the arc of my career, I have we intensify here.

00:37:13:10 – 00:37:46:03

Unknown

We're saying you got to intensify to is better than one. Sometimes three drugs are better than two. That's intensification. And you know we get that kind of your you know, your your first shot maybe it's your best shot. But I absolutely am a fan of D intensification as when it involves in a patient quality of life. You know there's no it's not helpful to be to the for us to say look your labs are great, your imaging is great, but your quality of life is miserable.

00:37:46:03 – 00:38:13:00

Unknown

You can't do what you want to do. And that's a very individual

discussion. Again, gets back to that shared decision making. I definitely offer d intensification in my patients. Some of them are very nervous about it, even though they're having side effects. Of course, if they're not having side effects, it's less of an issue unless it's cost, which is a prevalent issue globally and certainly in the U.S. as well.

00:38:13:06 – 00:38:43:14

Unknown

But if economic toxicity isn't an issue and side effects aren't an issue, I keep, I usually keep forward. Sometimes I'll even I'll still bring it up. But it's usually for patients who say, look, I just I just can't do anything anymore. I'm having so many side effects now. We don't we don't take an ostrich approach to it. We keep seeing the patient back and we monitor their lab values, their PSA, their test on a strong level, of course, subjectively.

00:38:43:14 – 00:39:14:13

Unknown

How are you doing? Are you having any new symptoms that could be related to the cancer and then periodic, you know, imaging tests? So and somebody like this who may have had wonderful resolution on conventional imaging, there's possibilities now for using some of the newer PSA pets for following a patient such as this. Oliver, can you just define what intermittent ADT really means and maybe also address the issue of what happens after you stop?

00:39:14:18 – 00:39:53:23

Unknown

Let's say this is your patient and he really, really wants to stop. So can you just define it intermittent And also what what you expect to happen to this gentleman after stopping? Sure. So intermittent is exactly what you would anticipate is just the use in a non continuous manner. Now, the thing is that there are a lot of different drugs which we have already broached and there's a lot of different intermittency and how you approach intermittent it with different drugs is a little bit of an interesting question because some of the drugs reverse fairly quickly.

00:39:54:02 – 00:40:29:20

Unknown

I mean, there's a little bit of a mention like the the oral antagonist that Neil had mentioned a little bit earlier or growth. So that particular medication reverses pretty quickly, as does abiraterone. By the way, the agonist reversed a little more slowly. And there a couple of factors that determine and we've actually published on this. Number one, if you want to recover your testosterone fast, it's a lot better if you're 38 years old and start out with a test of 800.

00:40:29:22 – 00:40:57:04

Unknown

If you're 83 years old. And your initial testosterone, by the way, I want to get initial testosterone before starting. Now, your initial testosterone is in the 150 range. But guess what? You stop the hormones and you don't recover very well. So how long you've been on the therapy also makes a difference. If you've been on site required for four months, that's different than if you've been on for 14 months or 24 months.

00:40:57:06 - 00:41:22:14

Unknown

The longer you're on it, the slower the recovery is. So what do you expect? You expect different things depending on the age of the patient, the baseline testosterone of the patient and the type of hormones that you're using and the duration of the hormones that have been used. So lots of variables go into what to expect very individuals to be, honestly.

00:41:22:16 - 00:41:42:15

Unknown

Yeah. Thank you. Thank you. But I sometimes describe it as a flawed factory. If you shut down the factory for a long time, I guess this is relevant with the UAW strike. If you shut it down for a very long time, it is not easy to get that factory up and running again. And the longer it shut down, the longer the longer it takes to get cars rolling off the assembly line.

00:41:42:15 - 00:42:04:15

Unknown

That's exactly the same with your testicles. The longer they down, the harder it is. And also the older you are, as you point out. Oliver. And then to the last question here, I'm sorry, I might just bring this up because the last thing is what when does hormone sensor become castration resistant? I mean, this is going to be the subject of our next webinar, which is out next week.

00:42:04:15 - 00:42:35:01

Unknown

It's in one month. But how do we define castration resistance? Like what actually happens, Oliver, That a hormone sensitive patient like this becomes castration resistant? How do we know? Well, you know, and Neal mentioned this a little bit earlier, the most sensitive indicator and this is true in the vast majority of cases is PSA. In the vast majority of cases, the PSA will begin to rise despite the test strobing test.

00:42:35:01 - 00:43:06:00

Unknown

Right now, the generally agreed upon definition of castrate testosterone is 1500 grams per deciliter. But guess what? That's

probably not a very good definition. It relates to some old assays, but if the testosterone is down, particularly in the less than 20 range and the PSA is rising, then you're castrate resistant. On occasion you could develop novel radiographic findings or even PSA PED findings in the absence of a PSA rise.

00:43:06:00 – 00:43:35:01

Unknown

But for the vast majority, low testosterone PSA rise is how we define the castrate resistant. Yeah. So. So how often, Neal, in order to monitor this, are you recommending patients get PSA while on ADT with the second drug? How often should they be getting a PSA or other lab tests and or seeing their doctors? Yeah, it's an important question.

00:43:35:01 – 00:43:55:24

Unknown

I mean, there's there's some, you know, important variables. You know, how close are you? What are your geographical constraints to get to your clinician? One of the things that I think is great now is the approval of telemedicine. A lot of our patients who are far, far from us, they can get their lab work in their house or in a nearby clinic.

00:43:56:01 – 00:44:20:11

Unknown

And if they're not having any subjective issues and don't need a physical exam, we can go over their lab work and see how they're feeling and even potentially go over some of their imaging. And so but to answer your question, you know, I think there's there's a range for patients who have metastatic hormone sensitive prostate cancer. I usually like to see them at least every 3 to 4 months.

00:44:20:13 – 00:44:40:17

Unknown

I rarely push it out to six months. Sometimes that happens. Patients still, you know, like to live their life. They want to travel. You know, they want to go cross-country. They want to take trips around the world or, you know, so I want to be sensitive to that. But as a general rule, I like to look at lab value and make sure I see how the patient's doing every 3 to 4 months.

00:44:40:17 – 00:45:01:01

Unknown

I'm I'm a little more liberal in patients who are earlier stages of the disease. And and but for us it's typically on a 3 to 4 month and certainly that's true once they develop resistant disease as well. Sometimes it's a lot you know you know it can be monthly or weekly if they're having problems. So that's part of.

00:45:01:03 – 00:45:23:04

Unknown

Go ahead, Oliver. But just one really quick comment. It depends in part about the response that you see. So one of the things we didn't really talk about, but it's important how low the PSA goes is going to predict how long the response is going to be. And if you have somebody who maybe started out at 150 and then they go to four, you think that's really good?

00:45:23:04 – 00:45:50:07

Unknown

It's not. That's not a very good response. That person needs close monitoring or they have a good response. But it's not as good as going to zero is what you made. Exactly. It's it sounds good, but it's not as good as if you went to less than 0.2. And it's a really good data to show that if you reach that less of 0.2 range or even less than 0.1, that you're probably going to respond for a long time.

00:45:50:09 – 00:46:23:14

Unknown

But if your PSA does not become undetectable or it Neda's out in the three four range, those durations of response are much shorter. So you have to monitor those more carefully. But, you know, I completely agree. You're absolutely right. There's great data. The lower the response, the better. But, you know, as I look at my so many patients and there's two things I've become very sensitive to, is how many physician visits that they do, You know, their cardiology, just the ophthalmologists, the you know, the primary care doctor.

00:46:23:14 – 00:46:50:10

Unknown

There's you know, there's like another half a dozen and then they're there. So there's the the poorly office visits and then the all the drugs they're taking. So you have to sometimes say, okay, I got to figure out a way here that people can get back to quality of life and enjoying life and becomes, you know, when we have a pandemic or, you know, gasoline shortages, some of these things get into that.

00:46:50:10 – 00:47:12:12

Unknown

What we'd like to do as opposed to the ideal scenario. Yeah, I mean, I think we have to empower the patients and their families. I think they should know what their own pieces are and unfortunately some anxiety comes with that. But but they should be paying attention because Oliver said something earlier that's very important, which is 95, 97% of the time the stories told in the PSA.

00:47:12:12 – 00:47:37:14

Unknown

So if the PSA either doesn't go down enough or starts to go up, then then you should be the first one to kind of understand how important that is. And Neal, the point about how often they have to come in, I

think especially with telehealth, but even with their own knowledge and with MyChart, if they get up like I often will because I practice in New York City, it's not easy to get to me.

00:47:37:16 – 00:47:58:11

Unknown

They will get their lab tests done, you know, on Long Island or New Jersey, you know, if I don't need to see them and I know their PSA is undetectable, I might not see them, you know, at three month visit, but they're still getting a lab test. And then I see them at the six month visit. So there's a lot of ways to make sure you, as the patient and the family member are empowered.

00:47:58:13 – 00:48:16:05

Unknown

But PSA still is. I always tell people PSA is a controversial screening test, but it's not controversial as a monitoring test. It still remains a really, really important way of monitoring. I'm going to get to a few of the questions. We have a lot of questions that came in before, and I'm going to let's do it like Rapidfire.

00:48:16:06 – 00:48:39:18

Unknown

Oliver, how long does prostate cancer typically respond to hormone treatment? It depends on where you start. So if you have typical metastatic disease with a fair number of lesions, I'll say there's pretty good data for something around two and a half years. But if you have a lower volume of disease, non metastatic disease that stretches out into the the eight and nine year period.

00:48:39:18 – 00:48:59:12

Unknown

So depends on how bad your cancer is in the beginning is going to determine how long it is you're going to respond. And there are media, those are medians which mean some people have very prolonged responses. The chairman of the Prostate Cancer Foundation, Michael Milken, has had advanced prostate cancer for 30 years. His cancer is still in remission.

00:48:59:12 – 00:49:35:22

Unknown

So really an inspiring story, Neal. One one person writes that her husband was diagnosed to no avail. At age 47. Is that common? Well, no. Typically it's a little bit older for the the the newly diagnosed, You know, hopefully he's still localized, maybe he's metastatic. Not really sure he's metastatic metastatic. So that's that's uncommon. That's in our if you look at epidemiological analyzes country by country that that would be in the single digit percentages.

00:49:35:22 – 00:50:02:10

Unknown

But you know unfortunately we do see it and so that's the type of patient who you'd want to be, you know, really aggressive with in terms of really kind of the proverbial kitchen sink at the disease. And that's probably someone who assuredly you'd want to have a combination. A conversation about triplet therapy, 80 a novel oral androgen receptor pathway inhibitor and r.p or not.

00:50:02:10 - 00:50:27:21

Unknown

And we have all these acronyms which confuse everybody, but they are oral drugs. The newest ones that block the androgen receptor, not the older generation ones that Oliver listed. And chemotherapy, I think six cycles of docetaxel, There's two wonderful trials that have been published that clearly support as long as the patient can tolerate chemotherapy. Most 47 year old certainly can.

00:50:27:23 - 00:51:03:10

Unknown

That would be a strong consideration. Yeah, I agree completely. It's not common, but there's an opportunity to be more aggressive because those are expected to live longer and they tolerate the treatments better. Oliver I want to mention very briefly the importance of genetic testing. You know what? I see that young guy with a bad disease. I wonder about the genome and as part of the routine today, routine for those patients diagnosed with metastatic disease, we get germline genetics.

00:51:03:12 - 00:51:26:12

Unknown

We look at understand whether or not the patient might have a broken may have, and they team all these different genes that can go wrong. And even though today that doesn't influence the treatments we choose, I think tomorrow it will be. And upon relapse, those could be important as well. So think about genetics when you have particularly young patients with their disease.

00:51:26:14 - 00:52:05:02

Unknown

Thank you for that. I just I have to just chime in. I'm even more aggressive about it than Oliver is. We've had presentations at ASCO at a way. I've got a publication that just came out in European Urologic Oncology. We're actually going to petition the IAU, a guidelines committee will probably petition NCC and to expand the the accessibility for ubiquitous everybody who gets prostate cancer diagnosis, even localized because the guidelines right now say if your grade group three, four or five, you should get a germline test.

00:52:05:04 - 00:52:29:10

Unknown

You don't get it if your grade group one and two and you have a negative family history. The problem is a lot of folks just don't know their family history and the germline testing has dramatically decreased in cost. Actually, one of the first wonderful times I heard that was at an annual PCF event. And then and so it used to be thousands of dollars.

00:52:29:10 – 00:52:55:11

Unknown

It's now literally a couple hundred dollars to get a germline test. We have that complete universal accessibility. If you have ovarian cancer, breast cancer, colorectal cancer, pancreatic cancer. So we and it's not just me, it's many others. We're really pushing to get germline testing for even localized disease. But that's an ongoing discussion. So let me just reemphasize a couple of points.

00:52:55:11 – 00:53:18:03

Unknown

You both brought up. First of all, we think everyone with metastatic disease, at a minimum, everyone listening to this call should get germline, which is your blood or your saliva. It's hereditary cancer testing. That means the DNA you inherited from your mother or father. And that's because especially in younger men, but also in others, it can tell you about what your risk was.

00:53:18:03 – 00:53:39:16

Unknown

And we all heard about BRCA1 and two, that's the most common one. But there are other risk factors that you can learn about that may have therapeutic consequences there, drugs that only work in that setting. The second thing is it is covered by many insurances. So even though the cost is not very high now it's come down for that germline or hereditary testing.

00:53:39:18 – 00:54:00:03

Unknown

It is covered by many insurances. So really look into that. The third thing is there is another kind of genetic testing, which is the testing of the tumor tissue, what we call somatic testing. And I'm just going to refer this group, the audience, to Becky. If Becky can put into the chat, we did a webinar on this exact topic, so please refer to that.

00:54:00:03 – 00:54:24:10

Unknown

It's taped and you can hear people talk about the genetic testing. Okay, So I'm going to ask Oliver to talk about Oligo metastatic disease. This patient that I described had seven spots. What if you only had one and what if he walked in the door with only one that's called Oligo metastatic? What does that mean? And how would you treat

that person differently, if at all?

00:54:24:12 - 00:54:54:04

Unknown

Yeah, great. Great question. William So Oligo, just for a translation means the few that we could talk about an oligarchy, in which case you may be ruled by a few, an oligopoly. So it just means that P typically have a range sort of conventionally a cut off at about five. But one of the things that's really critical, William, is it depends on how you detect that one or five.

00:54:54:06 - 00:55:21:16

Unknown

Is it conventional imaging or is its main pet two totally different categories of conventional imaging? Only if you ran the pet, you would probably find a lot more because it's just a more sensitive test. But just for a brief moment, let's use my pet as the standard. And let's say you find one metastases. And by the way, I saw that patient today in my quest.

00:55:21:18 - 00:55:48:09

Unknown

And what did I recommend? Well, first of all, for the patients initially being diagnosed, they have cancer in the prostate and we don't want to ignore the cancer in the prostate because they have metastatic disease. We need to treat the prostate. But in addition, we need to treat the area of metastatic disease. Now, this is where things get a little tricky because you don't quite have all the level one evidence that we would like.

00:55:48:11 - 00:56:18:10

Unknown

But nevertheless, in my practice I treat all known sites of disease typically with radiation, although sometimes surgery and radiation in combination. And in almost all likelihood, we're going to be using the hormonal therapies as well. So think about Oligo metastatic disease as an opportunity for us to eradicate all known areas of disease with therapy such as radiation or surgery, and put it into hormones, too.

00:56:18:12 - 00:56:45:03

Unknown

And by the way, sometimes we get beautiful responses that last for years and decades. You don't need to necessarily continue the hormones forever in those patients. You can use a more truncated variety. Thank you. We're getting a lot of questions about testosterone and particularly, let's say, in the patient where his testosterone, he stops the 80 and he stops the abiraterone and he's young.

00:56:45:03 - 00:57:09:14

Unknown

But two years later, his testosterone still not rising. Would you ever and let's say you do the scans. He has no cancers, PSA still low. Would you ever replace testosterone in a patient with the history of metastatic disease? Or what about testosterone replacement in other patients who have no evidence of disease? Neal Yeah, that's it's a very important question.

00:57:09:14 – 00:57:39:16

Unknown

It's, you know, because the reasons for wanting that would be for, you know, severe fatigue and lack of energy resulting in, you know, just depression, not being able to do your things that you like to do yard work, pickleball, golfing, running tennis, going out for a long walk and then sexual function. And it could be just the desire to recapture libido, desire, and it could be also to try to get back to that libido and, and good erections.

00:57:39:18 – 00:58:16:24

Unknown

And so it's it's an easier decision to make in a patient who doesn't have metastatic disease. And I definitely have a would and do perform testosterone supplementation for these patients. That's a much clearer route. I have also done it, believe it or not, in my patients who have known metastatic disease. But when it's again part of that shared decision about how bothered the patient is by their level of fatigue and what their tumor burden is, it's a very nuanced it's you have to be very careful with it.

00:58:17:01 – 00:58:40:16

Unknown

There are some other things that, you know, are involved in testosterone replacement. You may talk about it when you have your resistance panel, but I think it's a really good question. And I think that what we know is, you know, testosterone in and of itself, the data is pretty clear. It doesn't cause prostate cancer, but you have prostate cancer and clearly metastatic deposits.

00:58:40:16 – 00:59:08:13

Unknown

The worry, the risk is that you're going to recrudescence, you're going to put, you know, gasoline, so to speak, on to the fire. But I think as long as it's monitored very carefully and again, this is really the importance of shared decision making with the patient. I have these conversations with patients. Thank you. I know we're coming on time, but I wanted to give you both a chance to maybe give everyone a take home message.

00:59:08:15 – 00:59:35:02

Unknown

We have so many wonderful and important questions. We just can't get

to them all. But maybe one final message. We'll start with you, Oliver and then Neil, about what the audience should take home about metastatic disease. What's the most important thing for them to understand about treatment and their future? Oliver You know, gosh, I think if I had one take home message.

00:59:35:02 – 01:00:14:00

Unknown

William, it would be that if you have metastatic disease, you need expert care. You need the type of physician who understands prostate cancer, understands double or triple therapy, understands genomics, understands how to get metastatic disease. It was somebody who's got some experience in dealing with this type of patient. And if you're in the right hands, I think it can make a real difference simply because before you know it, William, we're going to have new advances, new progress, new therapies, new combinations.

01:00:14:02 – 01:00:33:16

Unknown

And if you don't keep up with the field, you can't keep up with all the advances that are inevitably going to occur with all the research occurring today. So get a good expert, stick with them. Don't be afraid of second opinions. But in the in the long run, you've got to find somebody you trust and want to work with closely.

01:00:33:18 – 01:00:56:06

Unknown

I feel really good words of advice, Neal. Yeah, I'll I'll I'll echo that second opinion. Third opinion. If you have a physician who tells you not to do that, you definitely need another physician. Knowledge is power, as they say, for the patient. And here's a just a quick take home and I'll stop it. It's been really fun to have this conversation.

01:00:56:08 – 01:01:38:03

Unknown

You know, in 2004, we got our first life prolonging therapy for patients with advanced prostate cancer. Almost 20 years later, 2023, we have now 14 life prolonging, life prolonging therapies, survival prolonging therapies for advanced prostate cancer. Now, that's incredible. Not to mention the the new imaging modalities, you know, better multidisciplinary care, getting more and more folks with different understandings of nutrition, exercise, you know, yoga, meditation, in addition, all these great therapeutics.

01:01:38:05 – 01:02:04:14

Unknown

So I would wholeheartedly endorse what Oliver said. You know, we you it's you can't be a general medical oncologist, a general urologist and do this well sub specialization is really where we're at. And it's true across the board in so many other aspects of health care, really

important words of wisdom. I've been doing this for 20, almost 25 years.

01:02:04:14 - 01:02:30:06

Unknown

I've known both of you for much of that time. We started in a time when there was nothing good that we could do and unfortunately patients would progress rapidly, and the exception was somebody who had a very prolonged response. Now that's becoming the rule. But we still have work to do. We need to be able to cure metastatic prostate cancer, and I'm optimistic that will happen in our lifetimes.

01:02:30:09 - 01:02:53:21

Unknown

But we have to keep working at it. And I think I'll end on that note of optimism, because we've been in this field together working as colleagues and and PCF has been supporting this kind of research and will continue to do so. So thank you very much for your time. Thank you to the audience for joining us. It's been a really enlightening conversation and have a very good night.

01:02:53:23 - 01:02:59:01

Unknown

Thanks for. I enjoyed it. Thanks, Neal. Thank you. Thank you both. They.